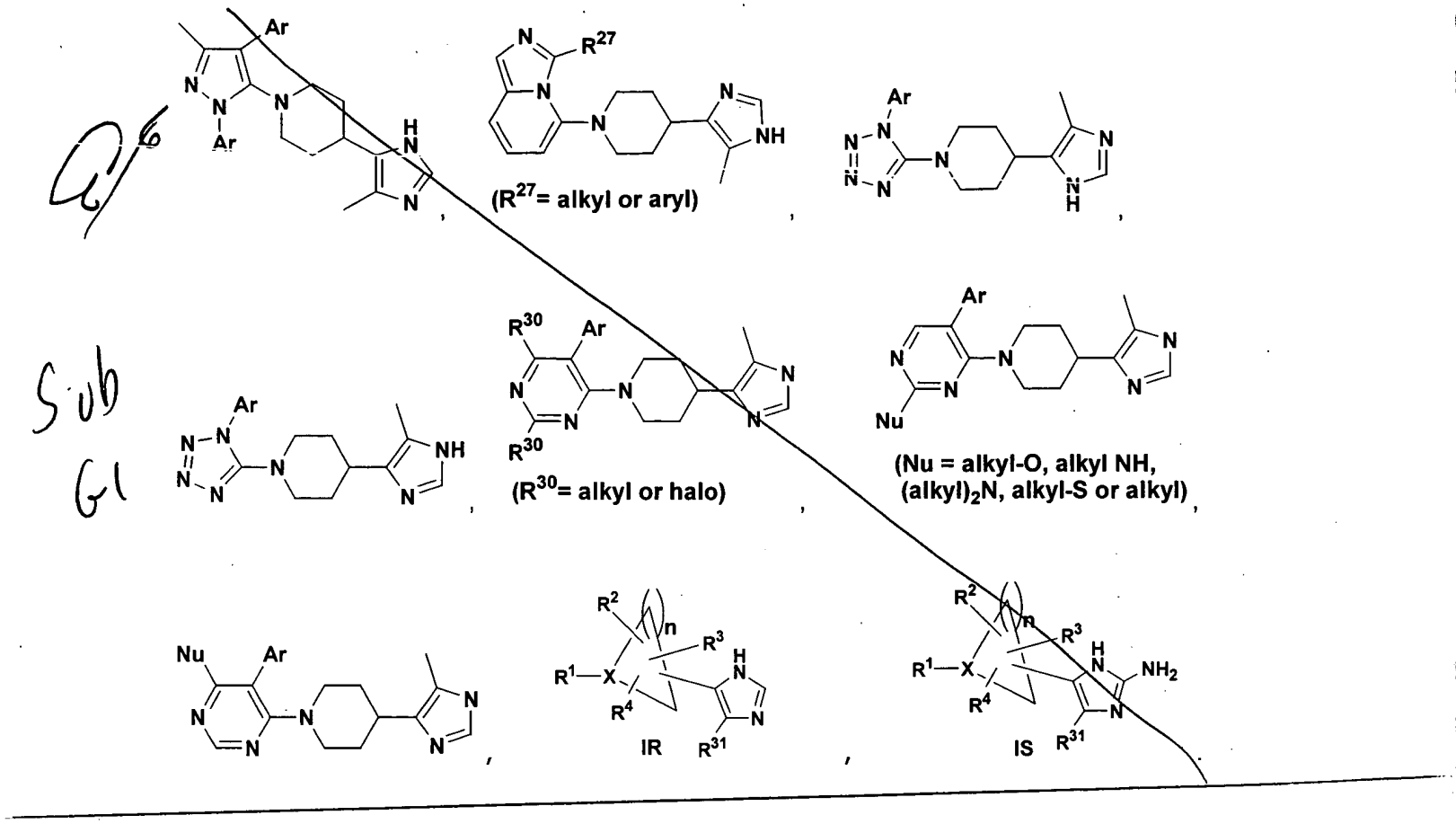


REMARKS

Claims 1 to 3, 6, 8 to 10, 14, 15, 17, 19, 20, 22, 24 to 31 and new Claims 63 to 74 are present for purposes of prosecution.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.

With regard to Applicants' election, that is compounds where X is N and n is 4, as suggested by the Examiner, the claims have been amended so that they now cover elected subject matter. Claims covering non-elected subject matter have been cancelled, but will be the subject of a divisional application yet to be filed.

Please note new Claim 64 wherein R^1 is defined as heteroaryl and Z is defined as heteroaryl.

New Claims 65 to 74 correspond to original Claims 6, 8, 9, 10, 14, 15, 19, 20, 22 and 25, respectively.

Claims 1 and 64 have been amended to include the definition of R^2, R^3 and R^4 as originally filed and as defined in original Claims 15 and 17.

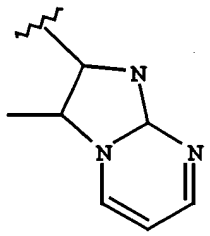
Claims 1-4, 6-10, 13-20, 22, 24-27, and 31 are rejected under 35 U.S.C. 112, first paragraph. The Examiner contends that

> "the specification, while being enabling for preparation of compounds wherein R^1 is heteroaryl and Z is imidazole, does not reasonably provide enablement for preparation and use of compounds wherein R^1 and Z are other than heteroaryl and imidazole, respectively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.
>
> "The nature of the invention in the instant application has claims which embrace a diversity of chemically and physically distinct compounds, wherein Z can be an unsubstituted or substituted, single or fused, heteroaryl group, containing one or more heteroatoms, etc. While many compounds are disclosed, there is insufficient guidance for preparing additional 'Na/H exchange inhibitors' which would be effective since the cited examples are drawn to a homogenous group of compounds not remotely commensurate in scope to applicants' claims. Only compounds wherein R^1 is monocyclic heteroaryl and Z is substituted imidazole have been made.
>
> "Furthermore, no biological testing data is provided the instantly claimed compounds. Examples should be of sufficient scope as to justify the scope of the claim. The definitions of the various R variables embrace many structurally divergent groups not represented at all in testing since testing for the instant compounds is not seen in the specification. Markush claims must be provided with support in the disclosure when the 'working examples' fail to include written description(s) which teach how to make and use Markush members embraced thereby in full, clear and exact terms. See In re Fouch, 169 USPQ 429.
>
> "This area of activity can be expected to be highly structure specific and unpredictable, as is generally true for chemically-based pharmacological activity. In view of the structural divergence in the claims, one skilled in the art could not reasonably extrapolate the activities of some of the claimed compounds to the other structurally divergent compounds embraced by the claims which have not been tested. In cases directed to chemical compounds which are being used for their physiological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. No reasonable assurance has been made that the instant compounds as an entire class have the required activities needed to practice the invention.
>
> "'Thus, factors such as "sufficient working examples', 'the level of skill in the art' and 'predictability' have been demonstrated to be sufficiently lacking in the instant case for the scope being claimed."

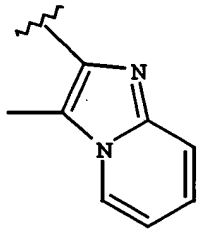
With respect to the Z group, the Examiner contends that the only compounds prepared includes Z as imidazole and R_1 as monocyclic heteroaryl.

Applicants respectfully refer the Examiner to the following Examples where a number of compounds are prepared which include Z as imidazole, alkylimidazole (Examples 128 to 156),

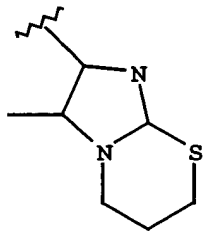
aminoimidazole (Examples 288 to 291), haloimidazole (Example 214d), amino(alkyl)imidazole (Examples 157 to 164), alkylcarbonylaminoimidazole (Examples 279 to 283, 285), alkoxycarbonylaminoimidazole (Examples 165 to 168), as well as various other heteroaryl groups including bicyclic groups, namely



(Example 265)



(Example 264)



(Example 266)

In addition, Applicants working examples include a large number of non-elected comounds where Z is other than imidazole. For example, please note Example 7 (aminooxadiazole), Example 8 (alkylthioimidazole), Examples 16 and 45 to 52 (aminothiazole) Example 28 (triazole), Example 29 (diaminopyrimidine).

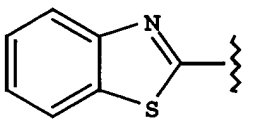
Accordingly, there is ample basis in the specification to support use of the term Z as heteroaryl in the claims.

With regard to the term "heteroaryl", Applicants refer the Examiner to page 17, lines 15 to 32 and page 18, lines 1 to 19 of the specification where the term "heteroaryl" is defined in clear and concise terms including ring size, type of heteroatoms, and nature of atoms as ring members.

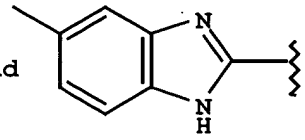
Use of the term "heteroaryl" in the claims is a widely accepted practice by the PTO as seen from the claims of the following U.S. patents:

5,543,542, 5,550,248, 5,561,146
5,567,841, 5,739,135, 5,760,246.

The Examiner maintains that the R^1 group in the compounds made is monocyclic heteroaryl. Please note Examples 129 and 130 where R^1 is

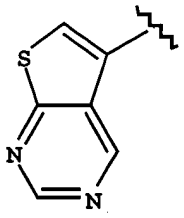


(Example 129) and



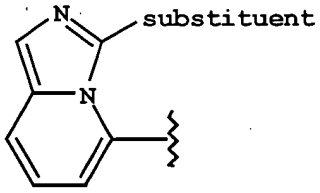
(Example 130)

In addition, please note Example 231 where R^1 is



, and

Examples 271 to 278 where R^1 is



Thus, Applicants include 11 working Examples of compounds where R^1 is other than a monocyclic heteroaryl.

In view of the foregoing, it is submitted that the 356 working Examples present provide ample basis to support the R_1 and Z substituents. Applicants have included a comprehensive disclosure on how to prepare all of the compounds covered by the present claims(please note pages 21 to 32) and how to use these compounds. Accordingly, it is submitted that Claims 1 to 4, 6 to 10, 13 to 20, 22, 24 to 27 and 3l are in compliance with 35 USC 112, first paragraph.

The Examiner rejects Claims 1-4, 6-10, 13-20, 22, 24-27 and 31 under 35 USC 112 first paragraph

> "because the specification, while enabling for preparation of compounds where R^1 is heteroaryl and Z is imidazole, does not reasonably provide enablement for preparation and use of compounds wherein R^1 and Z are other than heteroaryl and imidazole. The specification does not enable any person skilled in the art to which it pertains... to practice the invention commensurate in scope with these claims."

The above assertion by the PTO that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the Examiner's doubts. *In re Dinh-Nguyen et al*, (CCPA 1974) 492 F2d 856, 181 USPQ 46; *In re Bowen*, (CCPA 1974) 492 F2d 859, 181 USPQ 48; *In re Armbruster* (CCPA 1975) 512 F2d 676, 185 USPQ 152.

The Examiner has set out a number of broad general arguments as to the unpredictability of Applicants' compounds and invention; however, the Examiner has not seen set out any evidence or reasoning or arguments as to why he doubts whether Applicants' compounds may be prepared as disclosed and whether they have the utility as disclosed.

Applicants have set out 356 working Examples, at least 228 of which cover the elected invention and have included precise and reasonable definitions in the specification of all terms employed in the claims objected to by the Examiner and have defined such terms commensurate in scope with the specification.

Where broad terms, such as "heteroaryl" are supported by a reasonable number of examples and the Applicants have indicated that almost any heteroaryl would work, the Applicants should not be denied the use of such term or other terms merely because they are broad. *In re Grier* (CCPA 1965) 342 F2d 120, 144 USPQ 654.

Claims 1, 13, 22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention. The Examiner contends that

> "1). The use of 'heteroaryl' in the definitin of Z is unclear to the array of heteroatims, size of the rings, as well as nature of atoms as ring members. See In re Wiggins 179 USPQ 421 for certain terminology regarding heterocyclic ring systems.
>
> "2). 'Optionally substituted' throughout claim 1 is unclear as to the nature and number of substituent(s) intended.
>
> "3). In claims 13, 22, and 24, it is unclear what the zigzag symbol stands for. Does it stand for Z. Clarification is required."

With regard to the term "heteroaryl", as indicated, the definition of "heteroaryl" is set out in the specification at pages 17 and 18. Applicants include some 228 Examples of compounds having various heteroaryl groups for Z.

MPEP 706.03(d) indicates that:

"The fact that a claim is broad does not necessarily justify a rejection on the ground that the claim is vague and indefinite or incomplete."

Breadth alone is not indefiniteness. *In re Gardner et al* (CCPA 1970) 427 F2d 786, 166 USPQ 138. A broad claim which employs well-known language conventionally used in the art to which the invention pertains and which is of the same scope as the description of the invention as stated in the disclosure is not objectionable under the second paragraph of 35 USC 112, since it is neither "too broad" in the sense of embracing a concept not stated in the original disclosure nor is it vague or indefinite. *In re Kamal et al* (CCPA 1968) 398 F2d 867, 158 USPQ 320; *In re Borkowski et al* (CCPA 1970) 422 F2d 904, 164 USPQ 642. A rejection on undue breadth must be based on discrepancy between scope of disclosure and scope of claims. *In re Steinhauer et al* (CCPA 1969) 410 F2d 411, 161 USPQ 595.

The language employed in the claims is well-known and conventionally used in the chemical arts and is of the same scope as the description of the invention in the specification.

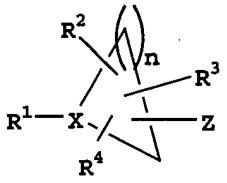
Accordingly, it is submitted that use of the term "heteroaryl" is acceptable under the PTO Rules of Practice.

With regard to 2). "optionally substituted" this term has been removed from the claims.

With regard to 3). Claims 13, 22, 24, and the zigzag symbol, Claims 22 and 24 have been amended so that they depend from Claim 14 which shows use of the zigzag symbol. The zigzag symbol does not designate "Z", but shows an open linker.

In view of the foregoing, it is believed that all formal objections have been overcome.

Applicants' invention as claimed in Claim 1 is directed to a compound having the structure

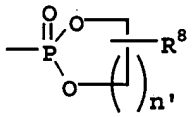


wherein n is 4;

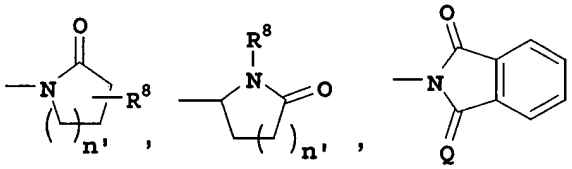
X is N;

Z is a heteroaryl group;

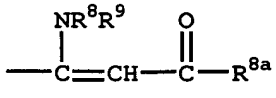
R^1 is alkynyl, alkoxy, alkenyloxy, alkynyloxy, (alkyl or aryl)$_3$Si (where each alkyl or aryl group is independent), cycloalkenyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylalkylamino, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, heteroarylamino, heteroaryloxy, arylsulfinyl, arylsulfonyl, thio, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, halogen, haloalkyl, polyhaloalkyl, polyhaloalkoxy, aminothio, aminosulfinyl, aminosulfonyl, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heteroarylaminocarbonyl, hydroxy, acyl, carboxy, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonyloxy, arylcarbonylamino, heteroarylcarbonyloxy, heteroarylcarbonylamino, cyano, nitro, alkenylcarbonylamino, alkynylcarbonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, alkynylaminocarbonylamino, arylaminocarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, aminocarbonylamino, alkylaminocarbonyloxy, alkoxycarbonylamino, l,l-(alkoxyl or aryloxy)$_2$alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring), $S(O)_2R^6R^7$, $-NR^6(C=NR^7)$alkyl, $-NR^6(C=NR^7)$alkenyl, $-NR^6(C=NR^7)$alkynyl, $-NR^6(C=NR^7)$heteroaryl, $-NR^8(C=NCN)$-amino,



pyridine-N-oxide,



(where Q is O or H_2 and n' is 0, 1, 2 or 3) or



; tetrazolyl, pyrazolyl, pyridyl, thiazolyl, pyrimidinyl, imidazole, oxazole, or triazole, $-PO(R^{13})(R^{14})$, (where R^{13} and R^{14} are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy);

R^6, R^7, R^8, R^{8a} and R^9 are the same or different and are independently hydrogen, alkyl, haloalkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, or cycloheteroalkyl;

and R^1 may be unsubstituted or substituted with from one to five substituents;

R^2, R^3 and R^4 are the same or different and are independently any of the groups originally set out for R^1 and may be optionally independently substituted with from one to five substituents, which may be the same or different;

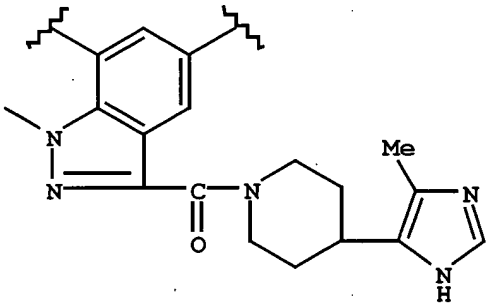
including pharmaceutically acceptable salts thereof, prodrugs thereof, and all stereoisomers thereof; with the provisos that (1) where Z is imidazol-4-yl, 5-alkylimidazol-4-yl or 5-cycloalkylimidazol-4-yl, then R^1 cannot be or include a benzoxazole, benzothiazole, or benzimidazole.

Please note new Claim 64 where R^1 is defined as "heteroaryl".

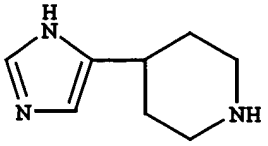
It is submitted that Applicants' invention as now claimed is patentable over all cited references each taken alone or in any combination.

Claims 1-4, 6-10, 12-19, 22, 24, 25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Even et al, Chem. Abstract 128:244047; or Schunack et al, Chem. Abstract 80:82801. The Examienr contends that "the instantly claimed compounds read on Even et al and Schunack et al compounds, i.e., the corresponding R^1 is H or heteroarylcarbonyl, Z is imidazole."

Even et al disclose compounds of the structure



and Even et al and Schunack et al disclose



As indicated by the Examiner, Even et al and Schunack et al disclose compounds where R^1 is H; Even et al disclose compounds where R^1 is heterorylcarbonyl. Claim 1 has been amended to delete H and heteroarylcarbonyl from the definition of R^1.

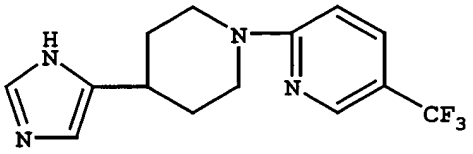
Claim 64 defines R^1 as heteroaryl.

In view of the above amendments to the definition of R^1, it is submitted that Applicants' compounds as claimed in Claims 1 to 3, 6, 8 to 10, 14, 15 17, 19, 22, 24, 25 and 31 and Claim 64 are patentable over Even et al and Schunack et al.

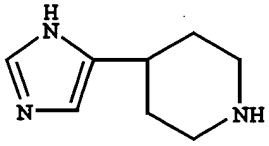
Claims 1-4, 6-10, 12, 13, 15-19, 22, 24, 25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Ganellin et al, Chem Abstract 123:198692. The Examiner contends that

> "the instantly claimed compounds read on the reference compound, see the enclosed copy of CAPLUS computer search report and the compounds, i.e., the corresponding R^1 is pyridine and Z is imidazole."

Ganellin et al disclose compounds of the structure



and



As indicated by the Examiner, Ganelli et al disclose compounds where "the corresponding R^1 is pyridine and Z is imidazole."

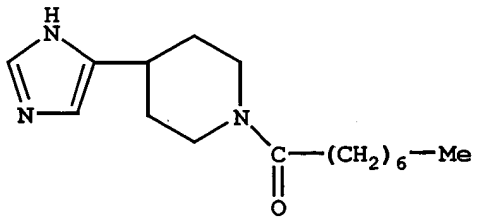
Claim 1 has been amended so that pyridyl and H are no longer encompassed by R^1.

In view of the foregoing, it is submitted that Claims 1 to 3,6,8 to 10, 14, 15, 17, 19, 22, 24, 25 and 31 and Claim 64 are patentable over Ganellin et al.

Claims 1, 2, 4, 6, 8-10, 12, 15, 16, 17, 22, 24, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Corbel et al, Chem Abstract 126:259445. The Examiner contends that

> "the instantly claimed compounds read on the reference compound, see the enclosed copy of CAPLUS computer search report and the compounds, i.e., the corresponding R^1 is alkyl and Z is imidazole."

Corbel et al disclose compounds which includes



As indicated by the Examiner, Corbel et al disclose compounds where R^1 is alkyl.

Claim 1 has been amended to delete alkyl from the definition of R^1.

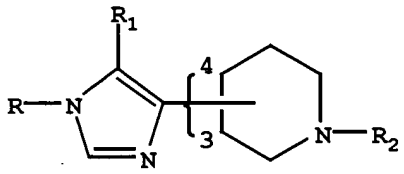
Claim 64 defines R^1 as heteroaryl.

In view of the above amendments to the definition of R^1, it is submitted that Applicants' compounds as claimed in Claims 1 to 3, 6, 8 to 10, 14, 15, 17, 19, 22, 24, 25 and 31 and Claim 64 are patentable over Corbel et al.

Claims 1, 2, 4, 6-10, 12, 14-16, 22, 24, 25 and 31 are rejected undeer 35 U.S.C. 102(b) as being anticipated by Arrang et al (US Patent 4,707,487). The Examiner contends that

> "Arrang teaches the compounds and composition of the instant invention (see Examples and compounds in Table 1)."

U.S. Patent No. 4,707,487 to Arrang et al discloses (4-imidazolyl)-piperidines of the formula

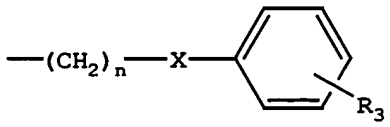


in which

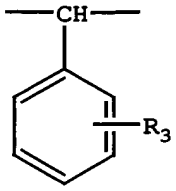
R_1 denotes a hydrogen atom or a methyl or ethyl group,

R denotes a hydrogen atom or a radical R_2, and

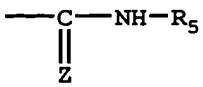
R_2 denotes a linear or branched alkyl group having 1 to 6 carbon atoms; a piperonyl group; a 3-(1-benzimidazolonyl)propyl group; a group of formula



in which n is 0, 1, 2 or 3, X is a single bond or alternatively -O-, -S-, -NH-, -CO-, -CH=CH- or



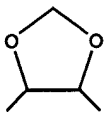
and R_3 is H, CH_3, halogen, CN, CF_3 or an acyl group $-COR_4$, R_4 being a linear or branched alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms or a phenyl group which can bear a CH_3 or F substituent; or alternatively a group of formula



in which Z denotes an O or S atom or a divalent group NH, N-CH_3 or N-CN and R_5 denotes a linear or branched alkyl group having 1 to 8 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms which can bear a phenyl substituent, a cycloalkyl (3 to 6 C) alkyl (1 to 3 C, linear or branched) group, a phenyl group which can bear a CH_3, halogen or CF_3 substituent, a phenylalkyl (1 to 3 C, linear or branched) group or a naphthyl, adamantyl or p-toluenesulphonyl group, as well as the pharmaceutically acceptable salts thereof.

R_2 in the Arrang et al compounds (correspond to Applicants' R^1 group) includes

(1) alkyl

(2) piperonyl (a phenylmethyl group having a  fused to the phenyl group -- thus piperonyl is an arylalkyl group)

(3) 3-(1-benzimidazolonyl)propyl (that is, a cycloheteroalkyl group)

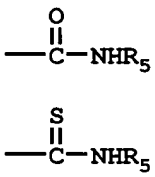
(4) (a) phenyl

(b) phenylalkyl

(c) phenyl-X- (where X is a bond, O, S, NH, CO, -CH=CH- or phenylmethylene)

(d) phenyl-X-alkyl

(5) acyl (COR_4- where R_4 is alkyl,cycloalkyl or phenyl

(6) 

where R_5 is alkyl, cycloalkyl, cycloalkylalkyl, phenyl, naphthyl, adamantyl or p-toluenesulfonyl.

Claim 1 has been amended to delete from the definition of R^1 the following: alkyl (which encompasses heteroaryl), arylalkyl, aryl, arylthio, arylamino, aryloxy, alkenyl, alkylaminocarbonyl, arylaminocarbonyl alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, heteroarylcarbonyl, 3-(1-benzimidazolonyl)propyl.

Thus, the amended definition of R^1 no longer encompasses any of the R_2 groups of Arrang et al.

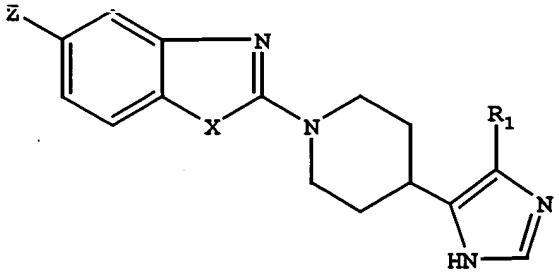
In view of the foregoing, it is submitted that Applicants' compounds as claimed in Claims 1 to 3, 6, 8 to 10, 14, 15, 17, 19, 22, 24, 25 and 31 and Claim 64 are patentable over Arrang et al.

Claims 1-4, 6-10, 12, 13, 15-18, 22, 24, 25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Jagham et al (US Patent 5,280,030). The Examiner contends that

"Jagham teaches the compounds and composition of the instant invention (see Examples

and compounds in Table 1 in col. 9)."

Jagham et al disclose a piperidine derivative of formula (I)



in which R_1 represents a hydrogen atom, a linear or branched (C_{1-6})alkyl group or a cyclo(C_{3-8})alkyl group, X represents an oxygen atom, a sulphur atom or a group of general formula N-R_3 in which R_3 is a hydrogen atom, or a linear or branched (C_{1-8})alkyl, cyclo(C_{3-6})alkyl, cyclo(C_{3-6})alkylmethyl, (C_{1-4})alkoxy-(C_{1-4})alkyl, phenyl, pyridin-4-yl, pyridin-3-yl, pyridin-4-ylmethyl or pyridin-3-ylmethyl group and Z represents a hydrogen or fluorine atom and acid addition salts thereof with pharmaceutically acceptable acids.

Thus, the Jagham et al bicyclic group linked to the N of the piperidine includes a benzimidazole, a benzthiazole or a benzoxazole.

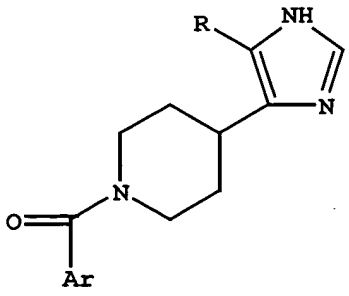
Please note that Claim 1 has been amended so that the R^1 group no longer includes a benzimidazole, a benzthiazole or a benzoxazole where the imidazole group is imidazole, alkylimidazole or cycloalkyl-imidazole.

In view of the foregoing, it is submitted that Claims 1 to 3, 6, 8 to 10, 14, 15, 17, 19, 22, 24, 25 and 31 and Claim 64 are patentable over Jagham et al (5,280,030).

Claims 1, 2, 4, 6, 8-10, 12, 15, 16, 22, 25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Jagham et al (US Patent 5,434,169). The Examiner contends that

"Jagham teaches the compounds and composition of the instant invention (see compounds in the Table, cols. 4-10)."

Jagham et al disclose a piperidine derivative of formula (I)



(I)

in which

R represents hydrogen, or unbranched or branched C_1-C_6 alkyl; and

Ar represents phenyl optionally substituted with one or more radicals selected from the halogens, amino, C_1-C_2 alkoxy and (C_3-C_6)cycloalkyl(C_1-C_2)alkoxy, or a heteroaryl group;

or a pharmaceutically acceptable acid addition salt thereof;

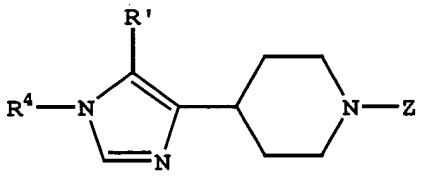
provided that when R is hydrogen Ar is not phenyl or 4-chlorophenyl.

Please note that Applicants' Claim 1 has been amended so that R^1 no longer includes arylcarbonyl or heteroarylcarbonyl.

In view of the above amendment to the definition of R^1, it is submitted that Applicants' compounds as claimed in Claims 1 to 3, 6, 8 to 10, 14, 15, 17, 19, 22, 24, 25 and 31 and Claim 64 are patentable over Jagham et al (5,434,169).

Claims 1, 2, 4, 6, 8-10, 12, 14, 16, 22, 24, 25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Durant et al (US Patent 5,663,350). The Examiner contends that "Durant teaches the compound and composition of the instant invention (see Example and compounds in the Table, cols. 15 and 16)."

Durant et al disclose compounds of the structure



wherein Z is

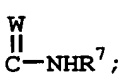
or R^2;

R' is H or C_1-C_4 alkyl;

R^1 is OR^2, $(CH_2)_nR^3$, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} cycloalkyl, C_1-C_{20} cycloalkenyl and C_1-C_{20} alkylaryl;

R^2 is C_1-C_6 alkyl, piperonyl or $(CH_2)_nR^3$;

R^3 is adamantyl methyl, C_1-C_{20} cycloalkyl, C_1-C_{20} cycloalkyl phenyl methylene, C_1-C_{20} dicycloakyl methylene, diphenyl methylene, Y-C_6H_4-R^5



R^4 is H,

or C_1-C_4 alkyl;

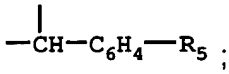
R^5 is H, CH_3, halogen, CN, CF_3 or COR^6;

R^6 is C_1-C_{20} linear or branched chain alkyl, C_1-C_{20} cycloalkyl, phenyl or phenyl substituted with 1-3 substituents selected from the group consisting of CH_3 or F;

R^7 is C_1-C_{20} linear or branched chain alkyl, C_1-C_{20} cycloalkyl phenyl methylene, C_1-C_{20} cycloalkyl alkyl methylene, C_1-C_{20} dicycloalkyl methylene, phenyl, phenyl substituted with 1-3 substituents selected from the group consisting of CH_3, halogen, C_1-C_3 alkyl (linear or branched);

X is S or O;

Y is a single bond or alternatively -O-, -S-, -NH-, -CO-, -CH=CH- or



W is O, S, NH, NCH_3 or NCN; and n=0-10.

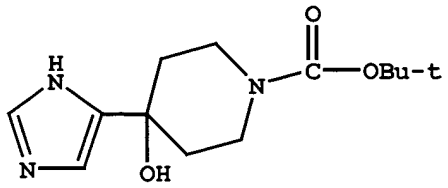
Applicants' Claim 1 has been amended so that R^1 no longer includes alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, alkyl, aryl, aryloxy, arylthio, arylalkyl, alkylaminocarbonyl or arylaminocarbonyl.

In view of the above amendments to the definition of R^1, it is submitted that Applicants' compounds as claimed in Claims 1 to 3, 6, 8 to 10, 14, 15, 17, 19, 22, 24, 25 and 31 and Claim 64 are patentable over Durant et al.

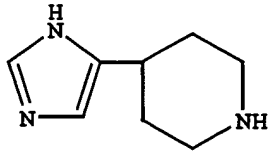
Claims 1, 2, 4, 6,10, 12, 14-16, 22, 24, 25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Lange et al, Chem Abstract 124:965601. The Examiner contends that

> "the instantly claimed compounds read on the reference compound, see the enclosed copy of CAPLUS computer search report and the compounds."

Lange et al disclose compounds of the structure



and



Claim 1 has been amended to delete H and alkoxycarbonyl from the definition of R^1.

In view of the above amendments to the definition of R^1, it is submitted that Applicants' compounds as claimed in Claims 1 to 3, 6, 8 to 10, 14, 15, 17, 19, 22, 24, 25 and 31 and Claim 64 are patentable over Lange et al.

Claims 1, 2, 4, 6-10, 12, 14-16, 22, 24, 25 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arrang et al (US Patent 4,707,487). The Examiner contends that

> "the reference teaches a generic group of compounds which embraces applicants' instantly claimed compounds. See formula I, col. 1 wherein R^1 is hydrogen, methyl or ethyl, R is hydrogen or R^2 wherein R^2 is alkyl, a 3-(1-benzimidazolonyl)propyl group or a group of formula $-(CH_2)_n$-X-phenyl-R^3, wherein n is 0-3, and X is a bond or a heteroatom or CH-phenyl, etc. The compounds are taught to be useful as pharmaceutical agents. The claims differ from the reference by reciting a specific species and/or a more limited genus than the reference. However, it would have nevertheless been obvious to one skilled I the art at the time of the invention to be motivated to select any of the species of the genus taught by the reference including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the specie of the genus would have similar properties and, thus, the same use as taught for the genus as a whole. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. See In re Susi, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in Merck & Co. V. Biocraft Laboratories, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989)."

Please note Applicants' arguments with regard to Arrang et al set out above.

As indicated hereinbefore, Applicants have amended the claims so that the R^1 group does not encompass or include any of the Arrang et al R^2 groups. Applicants do not claims the genus or any of the species disclosed in Arrang et al or any species within the scope of the Arrang et al genus.

There is no disclosure or suggestion in Arrang et al of any of the compounds as now claimed by Applicants.

With respect to Applicants' Claim 64, there is no disclosure or suggestion in Arrang et al of Applicants' compounds where R^1 is heteroaryl.

In view of the foregoing, it is submitted that Applicants' compounds as claimed are patentable over Arrang et al.

Claims 1-4, 6-10, 12-19, 22, 24, 25 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jagham et al (US Patent 5,280,030). The Examiner contends that

> "the reference teaches a generic group of compounds which embraces applicants' instantly claimed compounds. See formula I, Col. 1 wherein the substituents corresponding to R^1 of the present application is benzimidazole, benzathiazole, or benzoxazole, Z is hydrogen or

> fluorine, and the substituent corresponding to Z of the present application is substituted or unsubstituted imidazole, etc. The compounds are taught to be useful as pharmaceutical agents. The claims differ from the reference by reciting a specific species and/or a more limited genus than the reference. However, it would have nevertheless been obvious to one skilled in the art at the time of the invention to be motivated to select any of the species of the genus taught by the reference including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the specie of the genus would have similar properties and, thus, the same use as taught for the genus as a whole. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus."

Please note Applicants' arguments with respect to Jagham et al (U.S. Patent No. 5,280,030) set out above.

As indicated, Applicants have amended the claims so that the R^1 group does not encompass or include any of the Jagham et al (5,280,030) compounds. Applicants specifically exclude compounds where R^1 is benzimidazole, benzthiazole or benzoxazole, and Z is imidazole, alkylimidazole or cycloalkyl imidazole.

Applicants do not claim any compounds within the genus of Jagham et al. There is no disclosure or suggestion in Jagham et al of any of the compounds as now claimed by Applicants.

With respect to Claim 64, there is no disclosure or suggestion in Jagham et al of Applicants' compounds where R^1 is heteroaryl which excludes benzimidazole, benzthiazole and benzoxazole.

In view of the foregoing, it is submitted that Applicants' compounds as claimed are patentable over Jagham et al.

Claims 1, 2, 4, 6, 8-10, 12, 14-16, 22, 25 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jagham et al (US Patent 5,434,169). The Examiner contends that

> "the reference teaches a generic group of compounds which embraces applicants' instantly claimed compounds. See formula I, Col. 1 wherein R represents hydrogen or alkyl, Ar is optionally substituted phenyl or a heterocyclic group, etc. The compounds are taught to be useful as pharmaceutical agents. The claims differ from the reference by reciting a specific species and/or a more limited genus than the reference. However, it would have nevertheless been obvious to one skilled in the art at the time of the invention to be motivated to select any of the species of the genus taught by the reference including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the specie of the genus would have similar properties and, thus, the same use as taught for the genus as a whole. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within the genus."

Please note Applicants' arguments with respect to Jagham et al (U.S. Patent No. 5,534,169) set out above.

As indicated, Applicants have amended the claims so that the R^1 group excludes arylcarbonyl and heteroarylcarbonyl so that R^1 no longer encompasses or includes any of the Jagham et al $Ar-\overset{O}{\overset{\|}{C}}$ groups.

Applicants do not claim any compounds within the genus of Jagham et al. There is no disclosure of suggestion in Jagham et al of any of the compounds as now claimed by Applicants.

With respect to Claim 64, there is no disclosure or suggestion in Jagham et al of Applicants' compounds where R^1 is arylcarbonyl or heteroarylcarbonyl.

In view of the foregoing, it is submitted that Applicants' compounds as claimed are patentable over Jagham et al (5,434,169).

Claims 1, 2, 4, 6, 8-10, 12, 14, 16, 22, 24, 25 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Durant et al (US Patent 5,663,350). The Examiner contends that

> "the reference teaches a generic group of compounds which embraces applicants' instantly claimed compounds. See formula I, Col. 6 wherein Z is R^2 or C(X)-R^1 wherein X can be O, etc. The compounds are taught to be useful as pharmaceutical agents. The claims differ from the reference by reciting specific species and/or a more limited genus than the reference. However, it would have nevertheless been obvious to one skilled in the art at the time of the invention to be motivated to select any of the species of the genus taught by the reference including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the specie of the genus would have similar properties and, thus, the same use as taught for the genus as a whole. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus."

Please see Applicants' discussion of Durant et al as set out above.

As indicated, Applicants' claims as amended above no longer encompass any of the genus or species of compounds of Durant et al. Applicants have specifically excluded from R^1

alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, alkyl, aryl, aryloxy, arylthio, arylalkyl, alkylaminocarbonyl and arylaminocarbonyl.

Applicants do not claim any compounds within the genus of Durant et al. There is no disclosure of suggestion in Durant et al of any of the compounds as now claimed by Applicants.

With respect to Claim 64, there is no disclosure or suggestion in Durant et al of Applicants' compounds where R^1 is heteroaryl.

In view of the foregoing, it is submitted that Applicants' compounds as claimed are patentable over Durant et al.

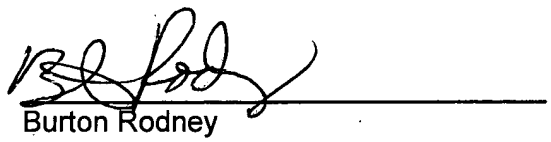
The Examiner indicates that

> "Claims 28-30 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. None of the prior art of record, nor a search in the pertinent art area teaches the exact species of the claims."

Claims 28 to 30 have been placed in independent form and now exclude all non-elected compounds and compounds encompassed by the prior art.

In view of the foregoing, it is submitted that Claims 1 to 3, 6, 8 to 10, 13, 15, 17, 19, 20, 22, 24 to 31 and new Claims 63 to 74 overcome all formal objections and are patentable over all cited prior art. Accordingly, it is believed that the above claims are in condition of allowance.

Respectfully submitted,



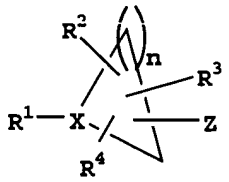
Burton Rodney
Attorney for Applicants
Reg. No. 22,076

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

Date: 1/16/02

MARKED-UP VERSION OF AMENDED CLAIMS

I. (Amended) A compound having the structure

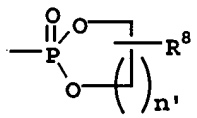


wherein n is 4 [an integer from 1 to 5];

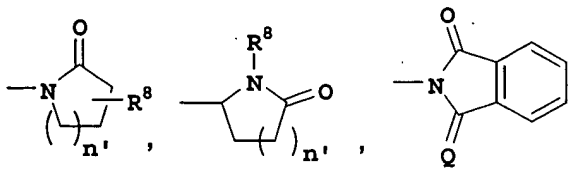
X is N [or C-R^5 wherein R^5 is H, halo, alkenyl, alkynyl, alkoxy, alkyl, aryl or heteroaryl];

Z is a heteroaryl group;

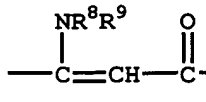
R^1 is [H, alkyl, alkenyl,] alkynyl, alkoxy, alkenyloxy, alkynyloxy, (alkyl or aryl)$_3$Si (where each alkyl or aryl group is independent), [cycloalkyl,] cycloalkenyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylalkylamino, [aryl, arylalkyl, arylamino, aryloxy,] cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, heteroarylamino, heteroaryloxy, [arylthio,] arylsulfinyl, arylsulfonyl, thio, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, halogen, haloalkyl, polyhaloalkyl, polyhaloalkoxy, aminothio, aminosulfinyl, aminosulfonyl, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, [alkylaminocarbonyl, arylaminocarbonyl,] heteroarylaminocarbonyl, hydroxy, acyl, carboxy, aminocarbonyl, [alkylcarbonyl, alkoxycarbonyl,] alkylcarbonyloxy, alkylcarbonylamino, [arylcarbonyl,] arylcarbonyloxy, arylcarbonylamino, [heteroarylcarbonyl,] heteroarylcarbonyloxy, heteroarylcarbonylamino, cyano, nitro, alkenylcarbonylamino, alkynylcarbonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, alkynylaminocarbonylamino, arylaminocarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, aminocarbonylamino, alkylaminocarbonyloxy, alkoxycarbonylamino, l,l-(alkoxyl or aryloxy)$_2$alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring), S(O)$_2$$R^6$$R^7$, -N$R^6$(C=N$R^7$)alkyl, -N$R^6$(C=N$R^7$)alkenyl, -N$R^6$(C=N$R^7$)alkynyl, -N$R^6$(C=N$R^7$)heteroaryl, -N$R^8$(C=NCN)-amino,



pyridine-N-oxide,



(where Q is O or H_2 and n' is 0, 1, 2 or 3) or

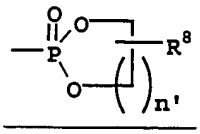


; tetrazolyl, pyrazolyl, [pyridyl,] thiazolyl, pyrimidinyl, imidazole, oxazole, or triazole, -PO(R^{13})(R^{14}), (where R^{13} and R^{14} are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy);

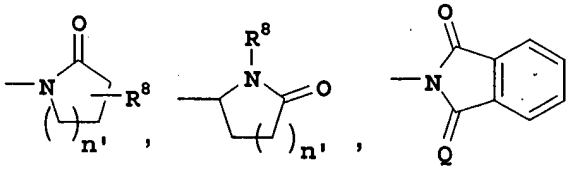
R^6, R^7, R^8, R^{8a} and R^9 are the same or different and are independently hydrogen, alkyl, haloalkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, or cycloheteroalkyl;

and R^1 may be [optionally] unsubstituted or substituted with from one to five substituents;

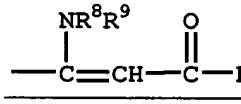
R^2, R^3 and R^4 are the same or different and are independently H, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, (alkyl or aryl)$_3$Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylalkylamino, aryl, arylalkyl, arylamino, aryloxy, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, heteroarylamino, heteroaryloxy, arylthio, arylsulfinyl, arylsulfonyl, thio, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, halogen, haloalkyl, polyhaloalkyl, polyhaloalkoxy, aminothio, aminosulfinyl, aminosulfonyl, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, hydroxy, acyl, carboxy, aminocarbonyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonyl, arylcarbonyloxy, arylcarbonylamino, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroarylcarbonylamino, cyano, nitro, alkenylcarbonylamino, alkynylcarbonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, alkynylaminocarbonylamino, arylaminocarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, aminocarbonylamino, alkylaminocarbonyloxy, alkoxycarbonylamino, l,l-(alkoxyl or aryloxy)$_2$alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring), S(O)$_2$$R^6R^7$, -N$R^6$(C=N$R^7$)alkyl, -N$R^6$(C=N$R^7$)alkenyl, -N$R^6$(C=N$R^7$)alkynyl, -N$R^6$(C=N$R^7$)heteroaryl, -N$R^8$(C=NCN)-amino,



pyridine-N-oxide,



(where Q is O or H_2 and n' is 0, 1, 2 or 3) or

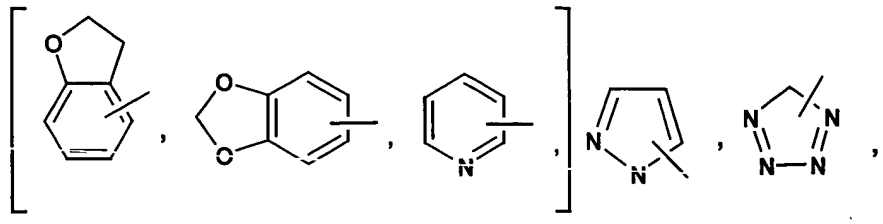


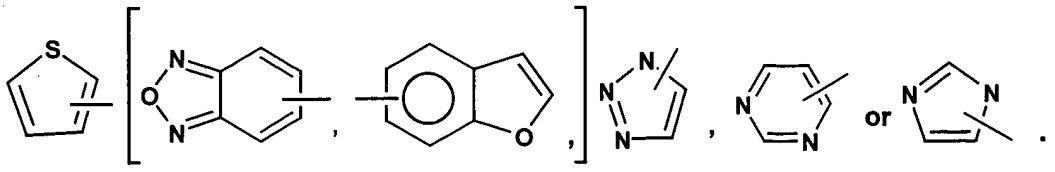
; tetrazolyl, pyrazolyl, pyridyl, thiazolyl, pyrimidinyl, imidazole, oxazole, or triazole, -PO(R^{13})(R^{14}), (where R^{13} and R^{14} are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy); [any of the groups set out for R^1] and may be optionally independently substituted with from one to five substituents, which may be the same or different;

including pharmaceutically acceptable salts thereof, prodrugs thereof, and all stereoisomers thereof; with the provisos that (1) where [X is N, n is 4, and] Z is imidazol-4-yl or 5-alkylimidazol-4-yl or 5-cycloalkylimidazol-4-yl, then R^1 cannot be or include a benzoxazole, benzthiazole, or benzimidazole and (2) R^1 is exclusive of 3-(1-benzimidazolonyl)-propyl [attached at the 4-position of the ring, then R^1 is other than phenyl or substituted phenyl].

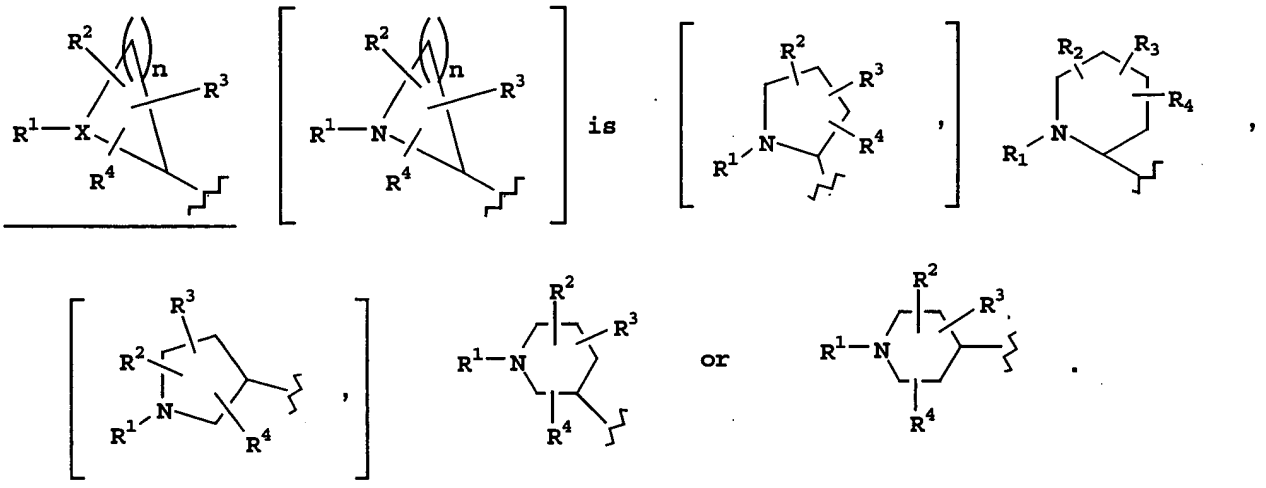
17. (Amended) The compound as defined in Claim I wherein [n is 4,] R^2 and R^3 are independently H or lower alkyl, and R^4 and R^5 are each H, and R^1 is [aryl or] heteroaryl.

19. (Amended) The compound as defined in Claim I wherein R^1 is [phenyl, halophenyl, dihalophenyl, alkylphenyl, nitrophenyl, dialkoxyphenyl, alkoxy(halo)phenyl, alkoxyphenyl, halo(nitro)phenyl, trifluoromethylphenyl, biphenyl, heteroarylphenyl, cycloheteroalkylphenyl, alkylthiophenyl, trialkoxyphenyl or halo(dialkoxy)phenyl, phenylalkyl,]

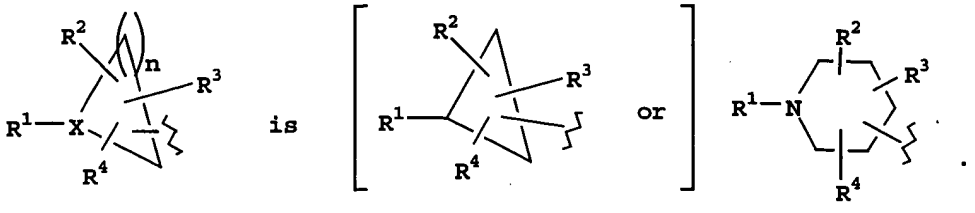




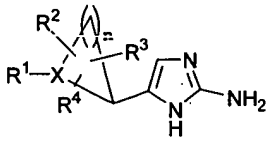
22. (Amended) The compound as defined in Claim [1] 14 wherein

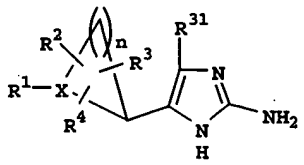


24. (Amended) The compound as defined in Claim [1] 14 wherein

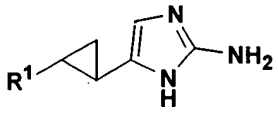


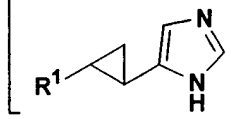
25. (Amended) The compound as defined in Claim 1 having the structure

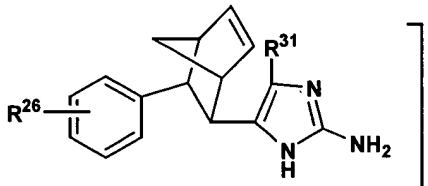




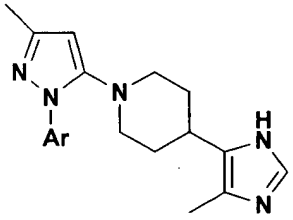
(R^{31} = alkyl, haloalkyl, aryl, heteroaryl)



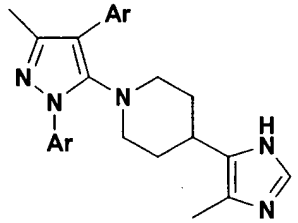


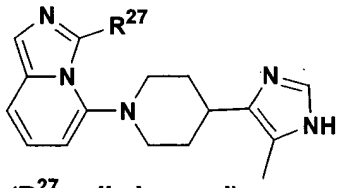


(R^{26}= halo, alkyl, aryl, heteroaryl, cyano or nitro)

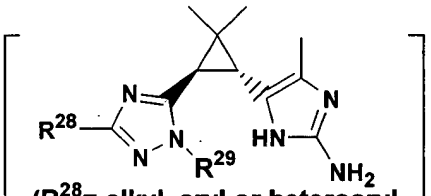


(Ar = aryl or heteroaryl)

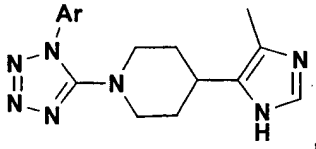


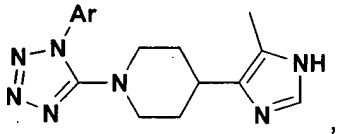


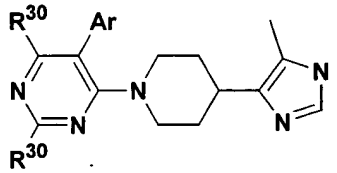
(R^{27}= alkyl or aryl)



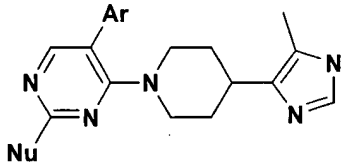
(R^{28}= alkyl, aryl or heteroaryl
R^{29}= alkyl, aryl, or heteroaryl)



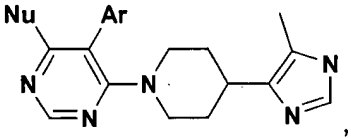


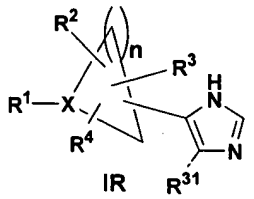


(R^{30}= alkyl or halo)



(Nu = alkyl-O, alkyl NH, $(alkyl)_2N$, alkyl-S or alkyl)





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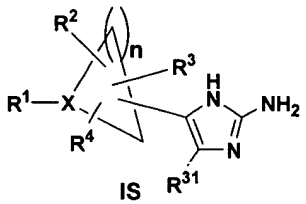
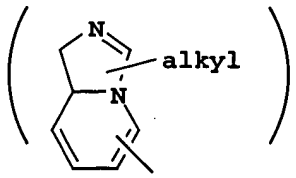


IS

26. (Amended) The compound as defined in Claim 1 wherein R^1 is [4-bromophenyl, 4-chlorophenyl, 3-bromophenyl, 3,5-dimethoxyphenyl, 4-methylphenyl, 2,4-dichlorophenyl, 3-nitrophenyl, 2-chlorophenyl, 3-chlorophenyl, 2,5-dimethylphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2,3-dimethoxyphenyl, 4-trifluoromethyl-phenyl, 3-trifluoromethoxyphenyl, 4-biphenyl, 2-bromo-4,5-dimethoxyphenyl, 4-methylthiophenyl, 3,4,5-trimethoxyphenyl, 4-fluorophenyl, 2-chloro-3,4-dimethoxyphenyl, 4-nitrophenyl, benzyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methoxyphenyl, 3-bromo-4-fluorophenyl, 2-fluoro-5-methoxyphenyl, 3-chloro-4-nitrophenyl, 2-fluoro-4-bromophenyl, 3-ethoxyphenyl, 3-trifluoromethylphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bistrifluoromethylphenyl, 4-fluorophenyl, 3-trifluorophenyl, 3-(N-pyrrolyl)phenyl, 3-(N-pyrrolidinyl)phenyl, 3-(N-pyrazolinyl)phenyl, 3-(N-imidazolyl)phenyl,] phenyltetrazole, 1-(2,4-dihalo-5-alkoxyphenyltetrazol-5-yl, alkylphenyltetrazole, halophenyltetrazol, 1-(2-alkoxy-5-halophenyl)tetrazol-5-yl, 1-(3-alkyl-4-halophenyl)tetrazol-5-yl, alkoxyphenyltetrazole, alkyl(halo)phenyltetrazole, alkoxy(halo)phenyltetrazole, alkoxy(alkyl)(halo)phenyltetrazole, phenyl-alkyl-pyrazole, alkoxyphenyl-alkyl-pyrazole, halophenyl-alkyl-pyrazole, alkyl(halo)phenyl-alkyl-pyrazole, alkylphenyl-alkyl-pyrazole, alkoxy(halo)phenyl-alkyl-pyrazole, alkoxy(alkyl)phenyl-alkyl-pyrazole, dihalophenyl-alkyl-pyrazole, dialkylphenyl-alkyl-pyrazole, alkoxyphenyl-alkyl-pyrazole, halophenyl-haloalkyl-pyrazole, alkoxyphenyl(alkyl)(halo)pyrazole, phenylpyrimidine, phenyl(halo)pyrimidine, diphenylpyrimidine, halophenyl(halo)pyrimidine, dihalopyrimidine, diphenyl(halo)pyrimidine, halo(phenyl)pyrimidine, dialkyl(halo)pyrimidine, dihalophenylpyrimidine, alkylphenylpyrimidine, alkoxyphenylpyrimidine, alkylphenyl(alkoxy)pyrimidie, dialkylphenyl(alkoxy)pyrimidine, alkyl(halo)phenyl(alkoxy)pyrimidine, alkoxy(halo)phenyl(alkoxy)pyrimidine, dihalophenyl(dialkylamino)pyrimidine, heteroaryl(dihalophenyl)pyrimidine, halophenylpyrimidine, alkoxy(phenyl)pyrimidine, haloalkoxyphenylpyrimidine, phenoxy(phenyl)pyrimidine, heteroaryl(phenyl)pyrimidine, dialkoxyphenylpyrimidine, dialkylphenylpyrimidine, cycloheteroalkyl(phenyl)pyrimidine, alkoxy(halo)phenylpyrimidine, cycloheteroalkyl(dihalophenyl)pyrimidine, halophenyl(alkoxy)pyrimidine, alkyl(halo)phenylpyrimidine, nitrophenylpyrimidine, dihalophenyl(alkoxy)pyrimidine, carboxyphenylpyrimidine, alkylcarbonylphenylpyrimidine,

naphthylpyrimidine, alkylthiophenylpyrimidine, [phenylpyridine, halophenylpyridine, alkyl(halo)phenylpyridine, dihalophenylpyridine, haloalkoxyphenylpyridine,] alkyl(halophenyl)triazole, alkyl(halo)phenyl-(alkyl)-triazole, alkylimidazopyridine



phenylimidazopyridine, halophenylimidazopyridine, dihalophenylimidazopyridine, alkoxyphenylimidazopyridine.

27. (Amended) The compound as defined in Claim I wherein

[X is CH or N;]

[n is 1 or 4;]

R^2 is CH_3 or H;

R^3 is CH_3 or H;

R^4 is H;

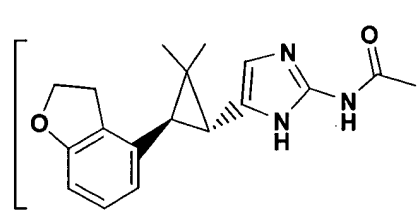
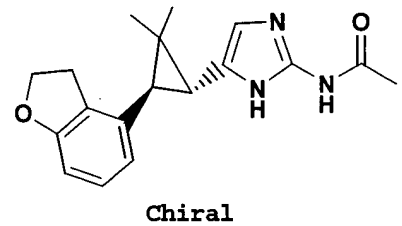
R^1 is [3-chlorophenyl, 3,5-dichlorophenyl, 3-chloro-4-fluorophenyl,] 2,3-dihydrobenzofuran-4-yl, [3-methyl-4-fluorophenyl, 3-phenyl-4-fluorophenyl, 2-fluoro-5-methoxyphenyl, 2-methoxy-5-chlorophenyl, 3-chloro-5-methoxyphenyl, 3-ethyl-4-fluorophenyl,] 1-phenyltetrazol-5-yl, [3-(2-fluorophenylcarbonylamino)pyridin-2-yl,]
1-(2,4-dichloro-5-methoxyphenyl)tetrazol-5-yl,
1-(3-chlorophenyl)tetrazol-5-yl,
1-(3-chloro-4-methyl)tetrazol-5-yl,
1-(3-methylphenyl)tetrazol-5-yl,
1-(2-chlorophenyl)tetrazol-5-yl,
1-(2-methoxy-5-chloro)tetrazol-5-yl,
[2-(propylcarbonylamino)phenyl,]
1-(3-methyl-4-chlorophenyl)tetrazol-5-yl,
1-(2-methoxy-5-chlorophenyl)tetrazol-5-yl,
1-(3-methoxyphenyl)tetrazol-5-yl,
1-(2-methoxy-5-chlorophenyl)tetrazol-5-yl,
1-(3-chlorophenyl)-3-methylpyrazol-5-yl,
1-(3-fluorophenyl)-3-methylpyrazol-5-yl,
1-(3-methoxyphenyl)-3-methylpyrazol-5-yl,

1-(3,5-dichlorophenyl)-3-methylpyrazol-5-yl,
1-(3-chlorophenyl)-3-ethylpyrazol-5-yl,
1-(3-chloro-4-methylphenyl)-3-methylpyrazol-5-yl,
1-(2,4-dimethylphenyl)-3-methylpyrazol-5-yl,
1-(3-chloro-4-fluorophenyl)-3-methylpyrazol-5-yl,
1-(3-trifluoromethylphenyl)-3-methylpyrazol-5-yl,
1-(3-chlorophenyl)-3-trifluoromethylpyrazol-5-yl,
1-(3-methylphenyl)3-methylpyrazol-5-yl,
1-(3-chlorophenyl)-3-ethylpyrazol-5-yl,
5-(3-chloro-4-fluorophenyl)pyrimidin-4-yl,
5-(2-chlorophenyl)pyrimidin-4-yl,
5-(3-methylphenyl)pyrimidin-4-yl,
5-(3-trifluoromethylphenyl)pyrimidin-4-yl,
5-(2,4-dichlorophenyl)pyrimidin-4-yl,
5-(2,5-dimethylphenyl)pyrimidin-4-yl,
5-(3,4-dichlorophenyl)pyrimidin-4-yl,
5-(2,3-dimethylphenyl)pyrimidin-4-yl,
5-(2-methoxy-5-chlorophenyl)pyrimidin-4-yl,
5-(2-methoxy-5-fluorophenyl)pyrimidin-4-yl,
5-(3-methyl-4-fluorophenyl)pyrimidin-4-yl,
[3-(3-methyl-4-fluorophenyl)pyridin-2-yl,]
[3-(3-chloro-4-fluorophenyl)pyridin-2-yl,]
[3-(3-trifluoromethoxyphenyl)pyridin-2-yl,]
5-(3-chloro-4-fluorophenyl)-2-methoxy-pyrimidin-4-yl,
5-(3-chloro-4-fluorophenyl)-2-dimethylamino-pyrimidin-4-yl,
5-(3-chloro-4-fluorophenyl)-2-morpholinyl-pyrimidin-4-yl,
1-(3-chlorophenyl)-3-methyltriazol-5-yl,
1-(3-chloro-4-methylphenyl)-3-methyltriazol-5-yl,
5-(2,5-dichlorophenyl)pyrimidin-4-yl,
5-(3-chlorophenyl)pyrimidin-4-yl,
5-(3-trifluoromethoxyphenyl)pyrimidin-4-yl,
5-(2-chlorophenyl)-2-methoxypyrimidin-4-yl,
5-(3-chlorophenyl)-2-methoxypyrimidin-4-yl,
5-(3-trifluoromethylphenyl)-2-methoxypyrimidin-4-yl,

5-(2,4-dichlorophenyl)-2-methoxypyrimidin-4-yl,
5-(3-methylphenyl)-2-methoxypyrimidin-4-yl,
5-(2,5-dimethylphenyl)-2-methoxypyrimidin-4-yl, or
5-(3-methyl-4-fluorophenyl)-2-methoxypyrimidin-4-yl;

Z is 2-amino-5-methyl-imidazol-4-yl,
2,5-dimethylimidazol-4-yl, 2-amino-5-ethyl-imidazol-4-yl, 2-amino-5-isopropyl-imidazol-4-yl, 2-aminocarbonylamino-5-methyl-imidazol-4-yl, 5-methyl-imidazol-4-yl, imidazol-4-yl, or 4-methylimidazol-5-yl.

28. (Amended) [The] A compound [as defined in Claim 1] having the strucutre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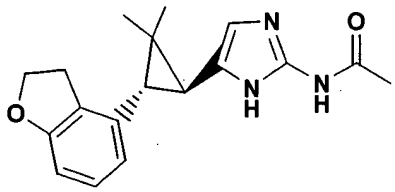
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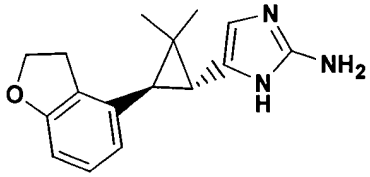
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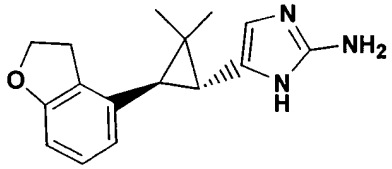
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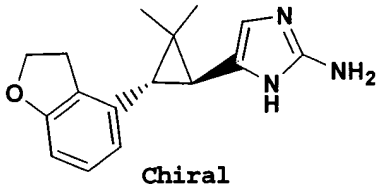
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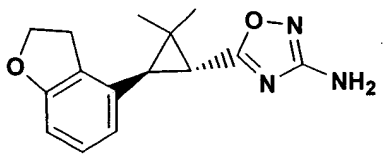
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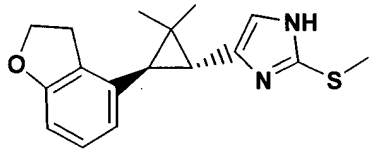
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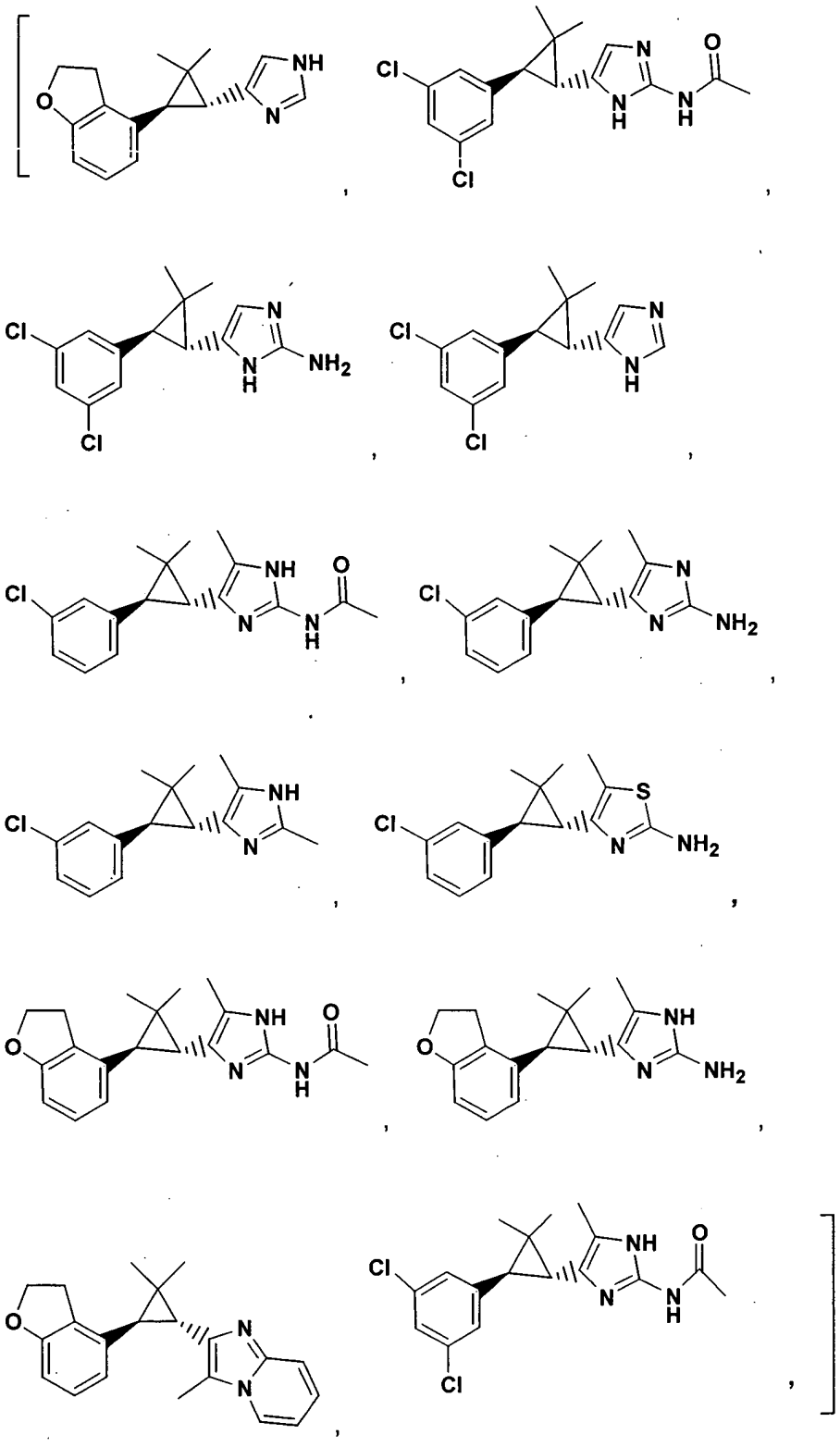

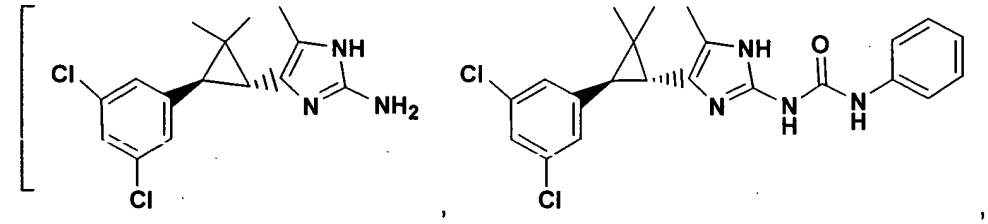

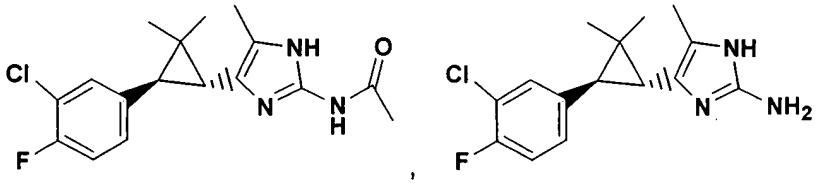

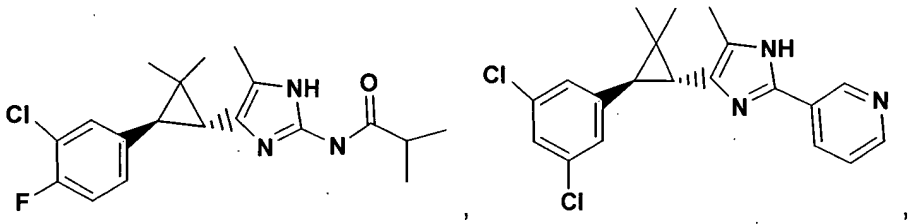

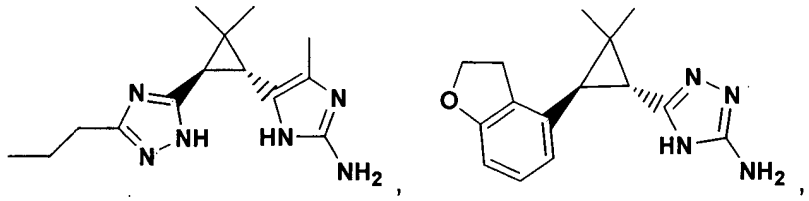

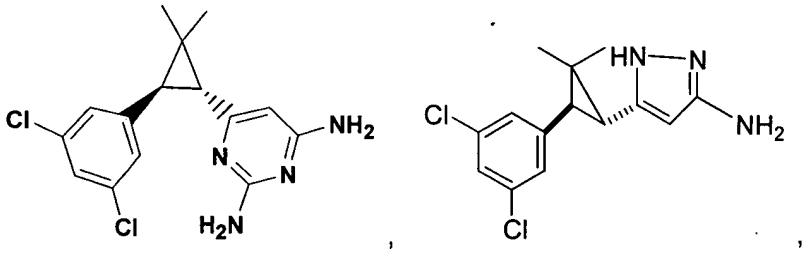

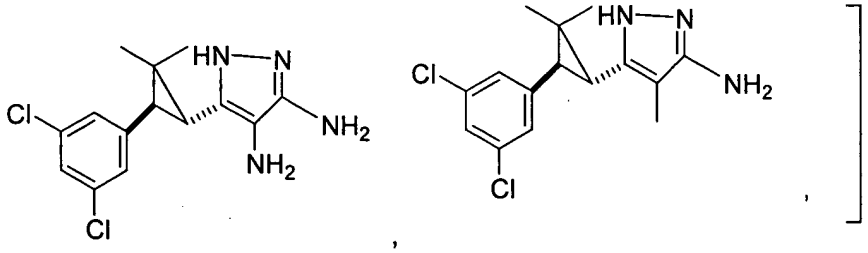

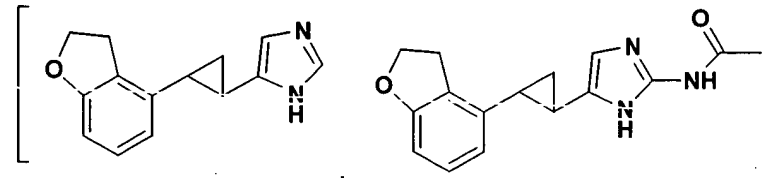

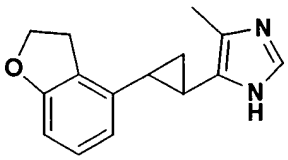
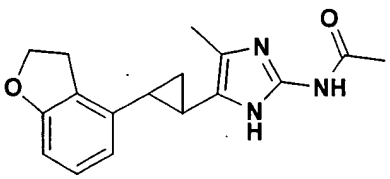
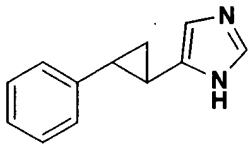
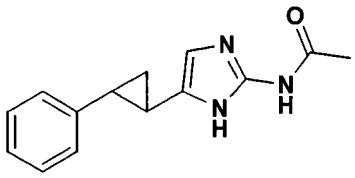
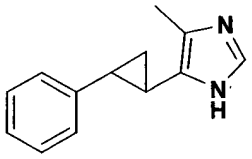
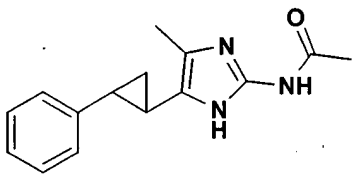
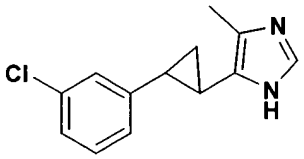
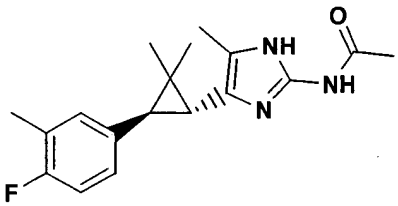
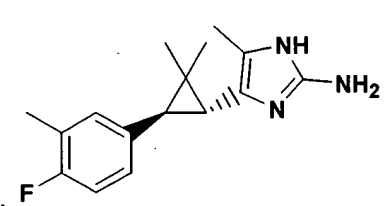
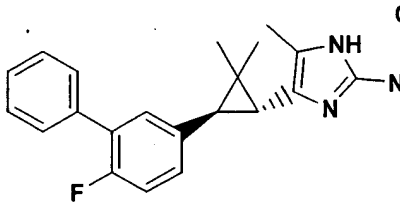
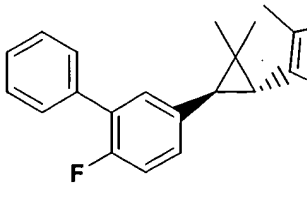

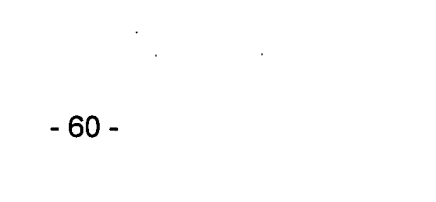

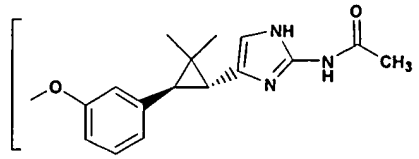

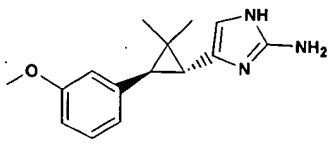

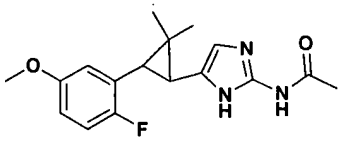

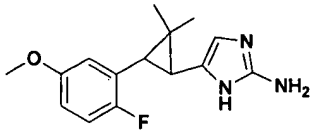

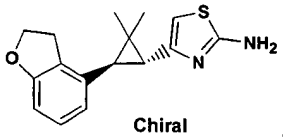
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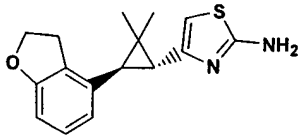

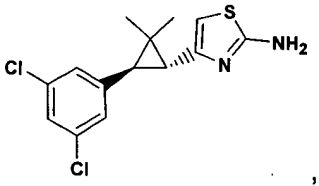

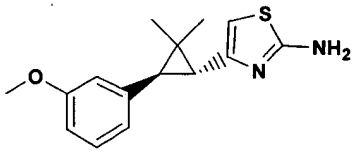

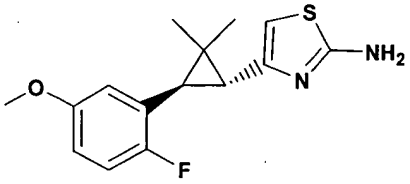

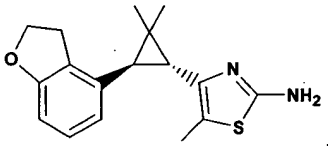

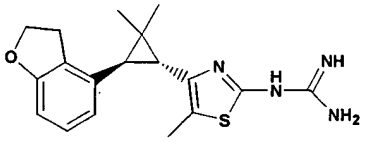

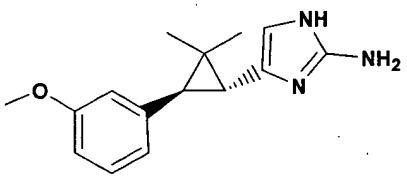

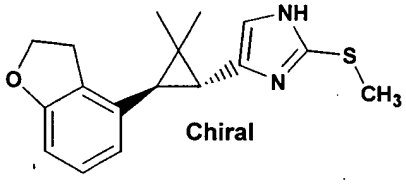
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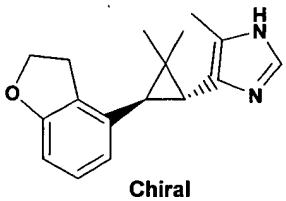
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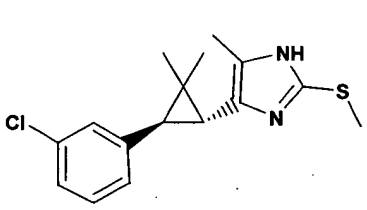

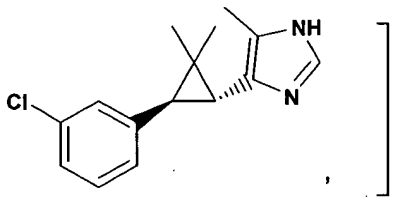

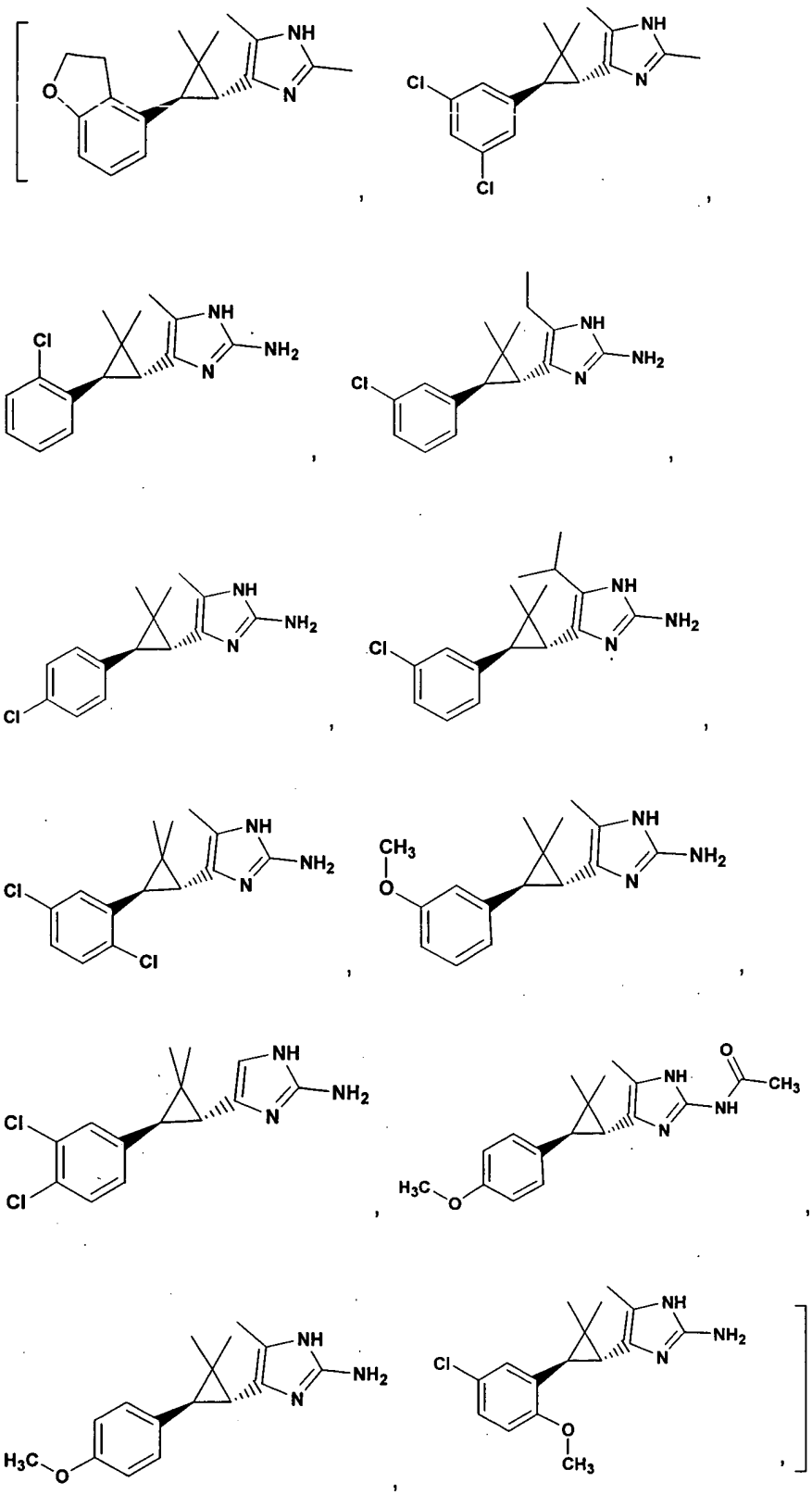

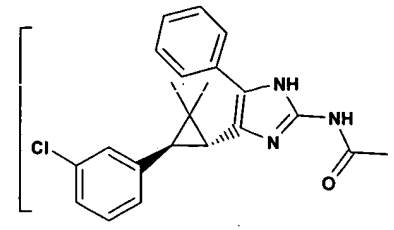
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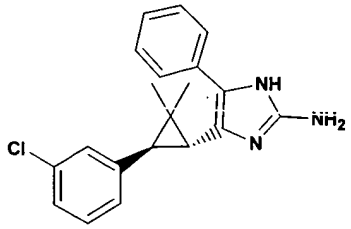
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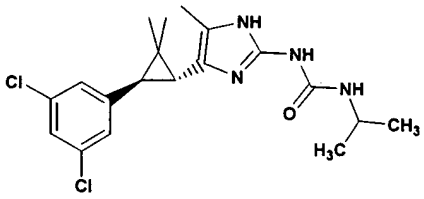
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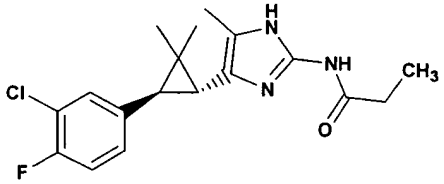
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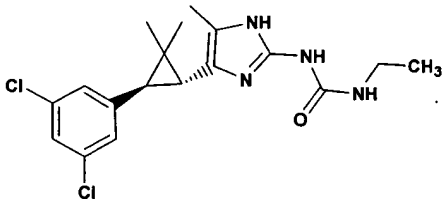
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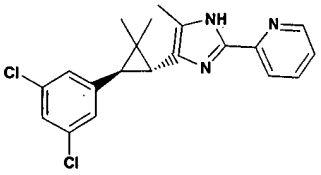
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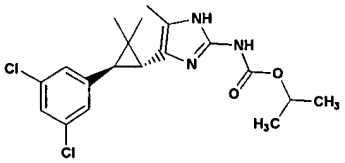
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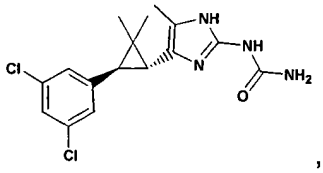
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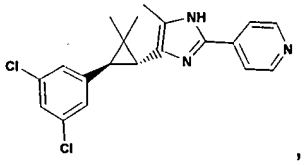
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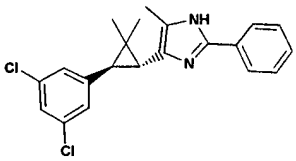
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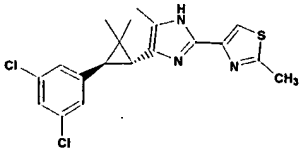
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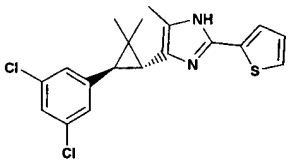
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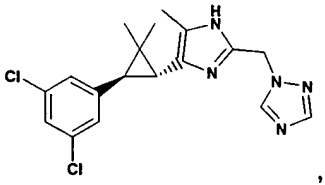
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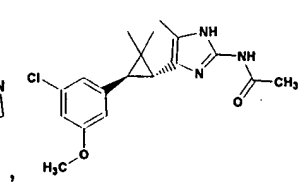
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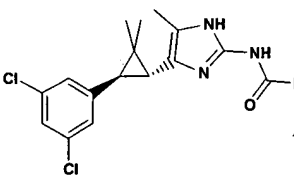
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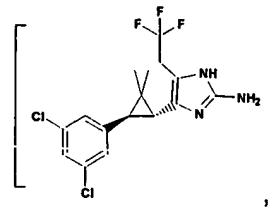
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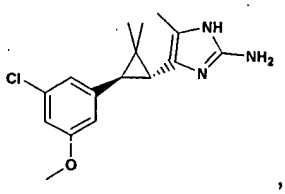
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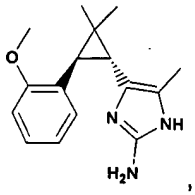
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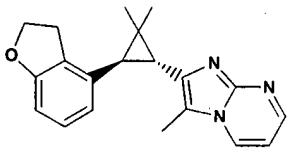
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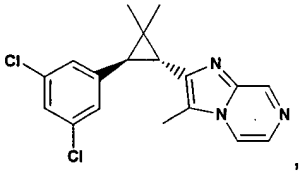
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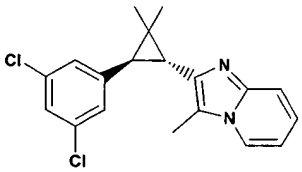
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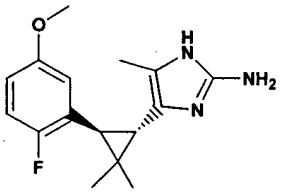
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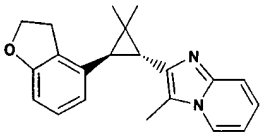
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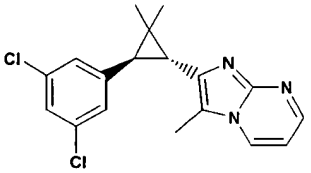
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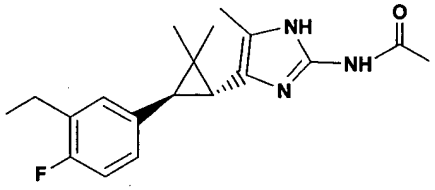
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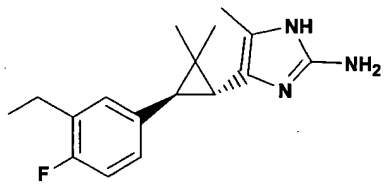
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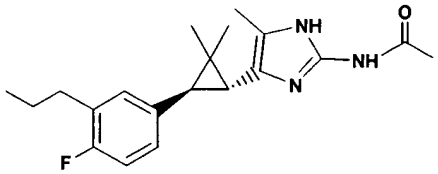
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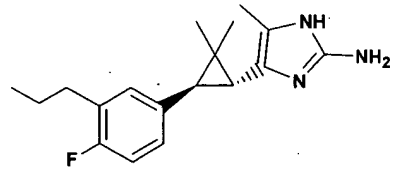
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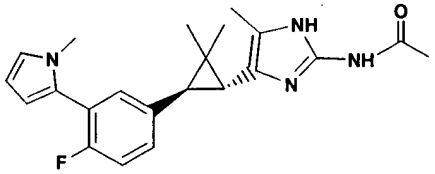
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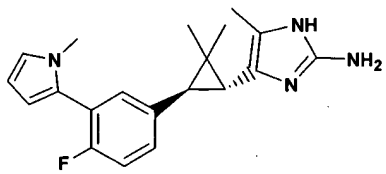
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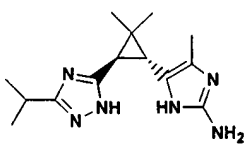
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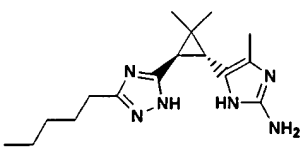
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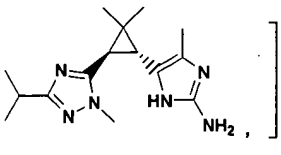
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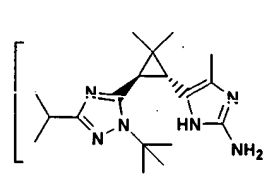

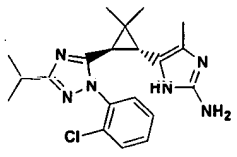

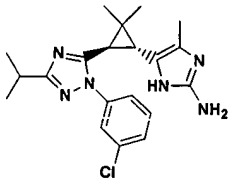

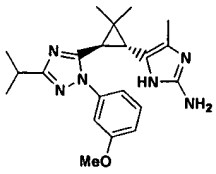

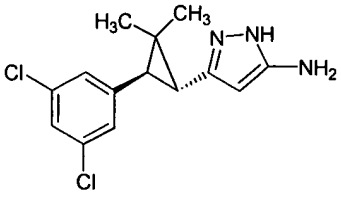

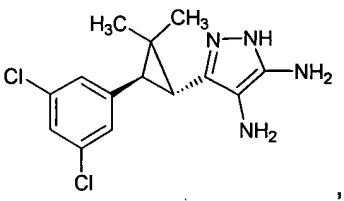

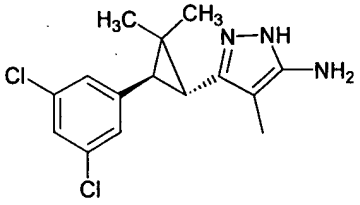

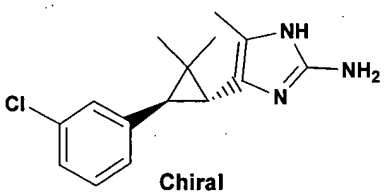
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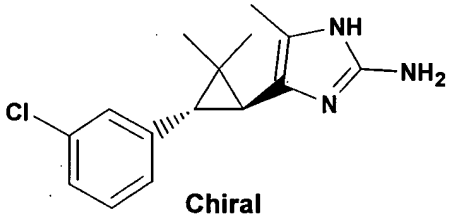
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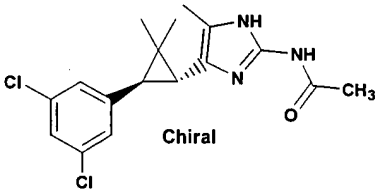
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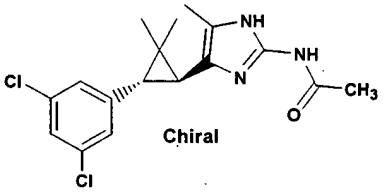
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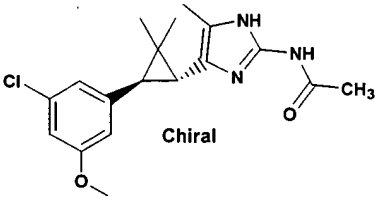
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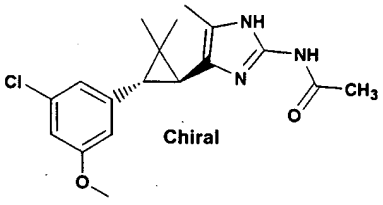
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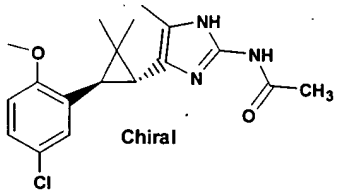
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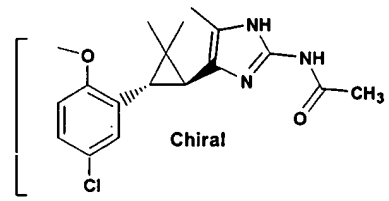
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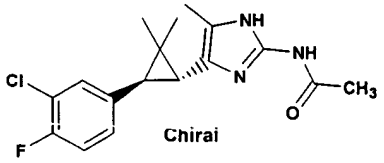
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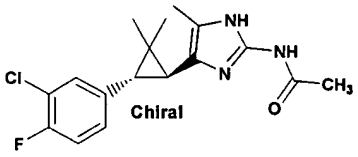
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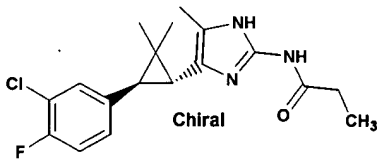
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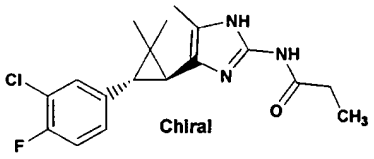
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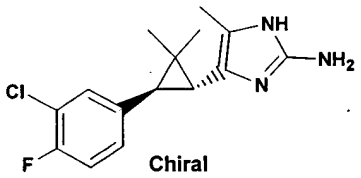
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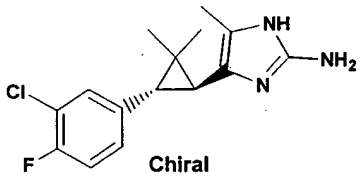
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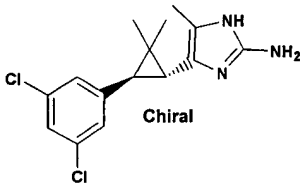
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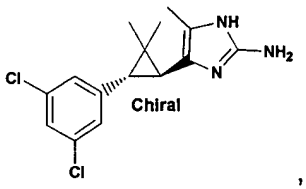
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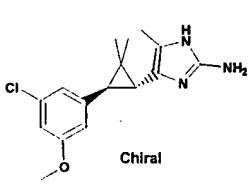
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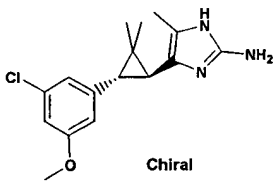
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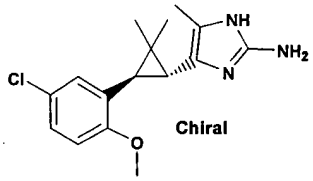
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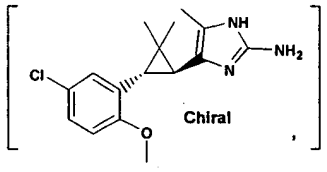
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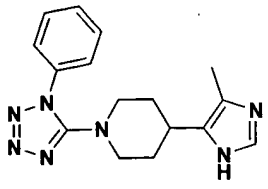
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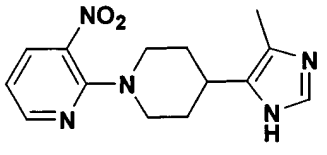
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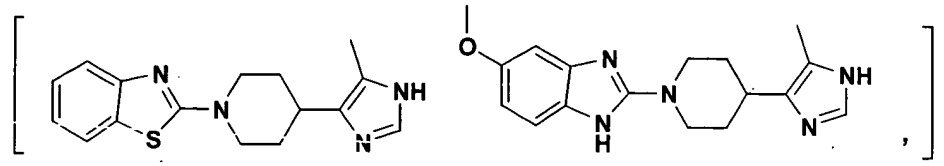
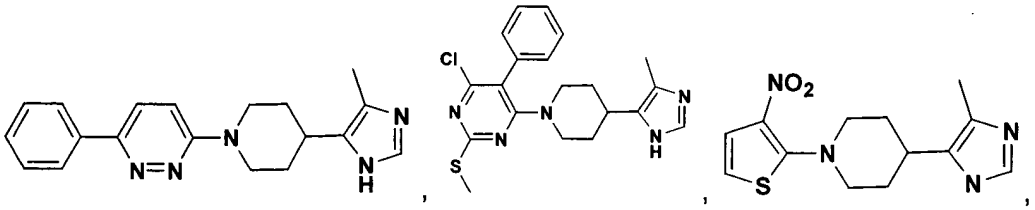
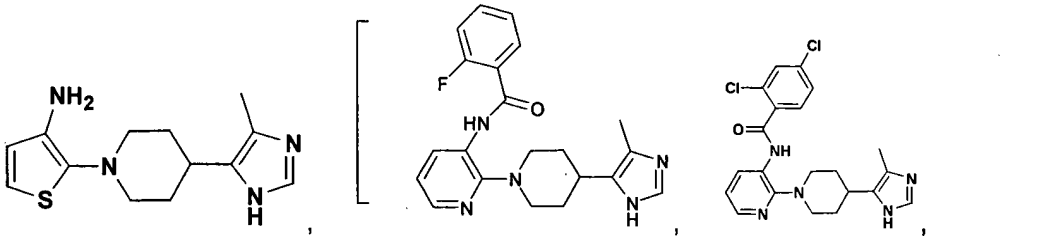
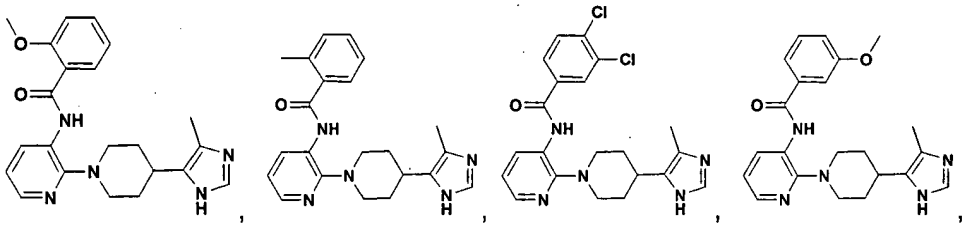
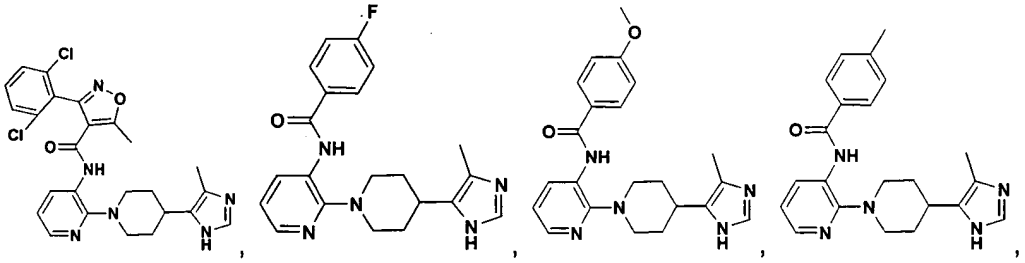
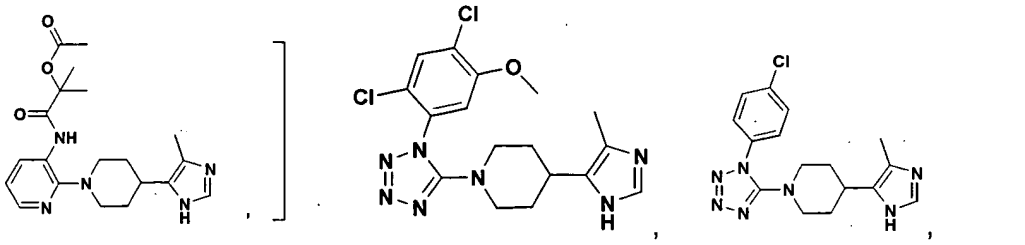


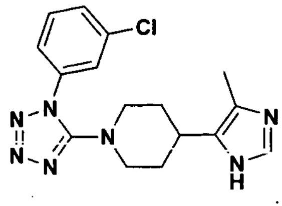
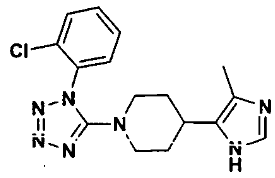
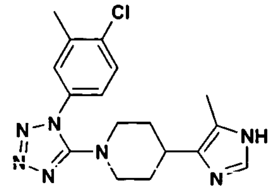


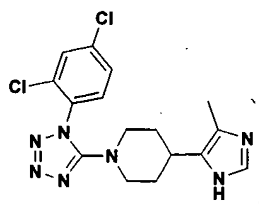
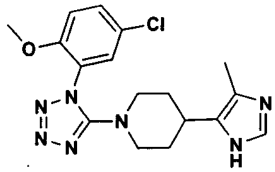
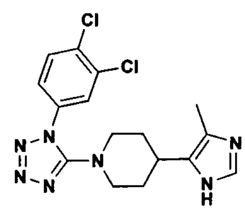


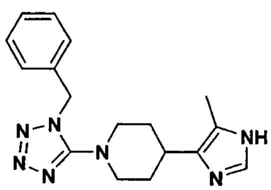
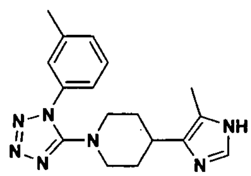
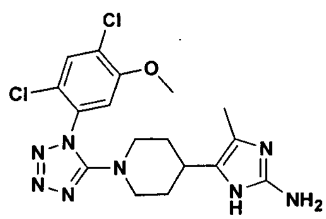


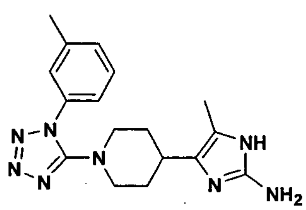
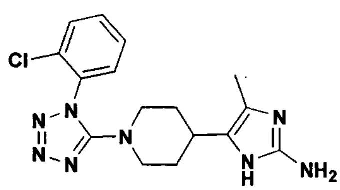
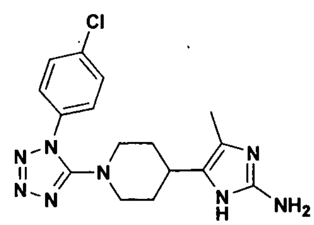


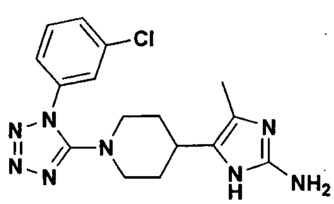
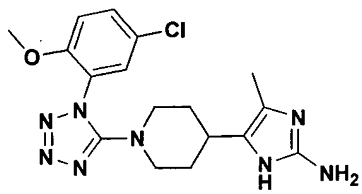
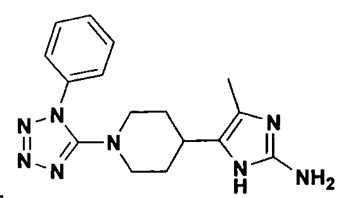


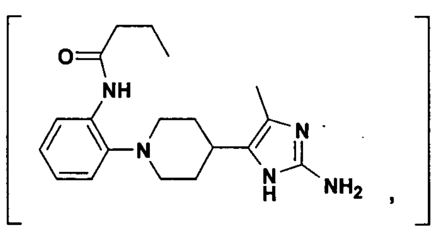
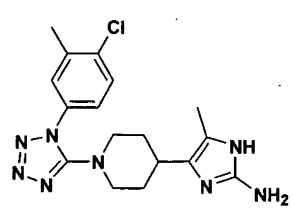
 ,
 ,
 ,

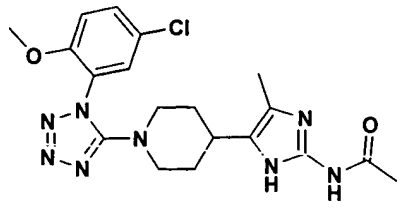
 ,
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,


 ,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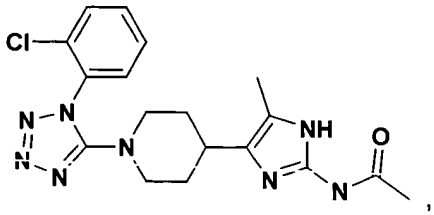
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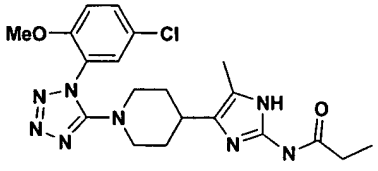
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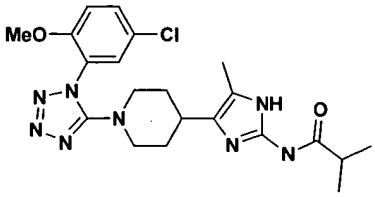
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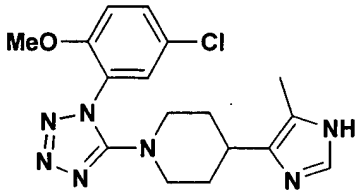
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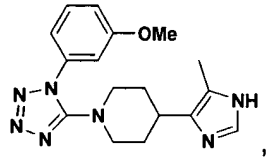
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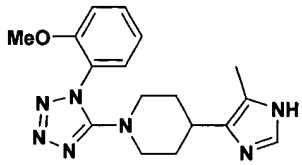
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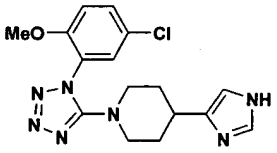
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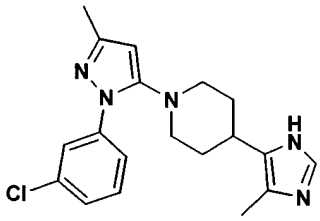
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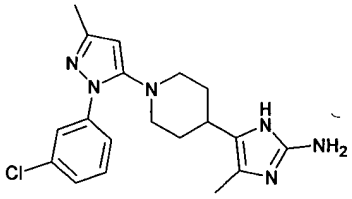
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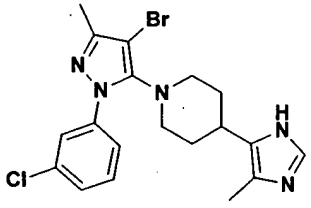
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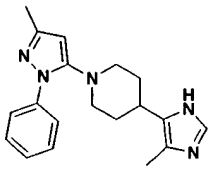
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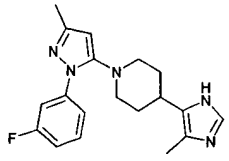
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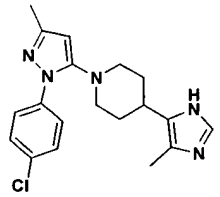
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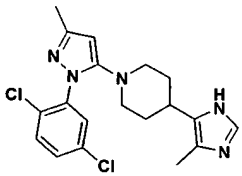
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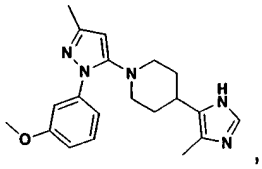
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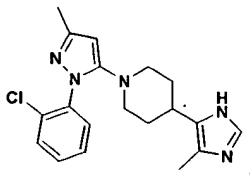
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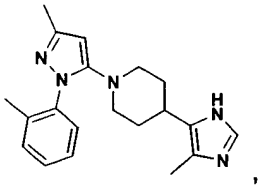
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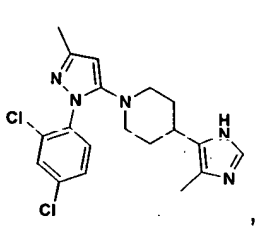
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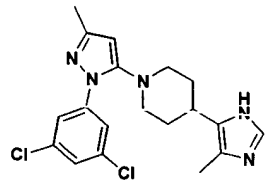
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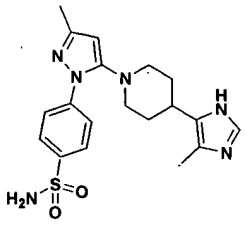
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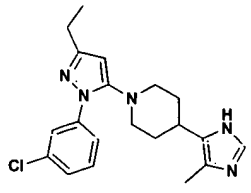
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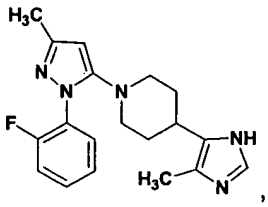
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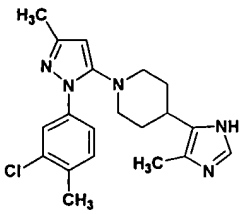
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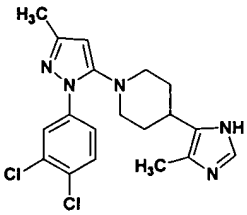
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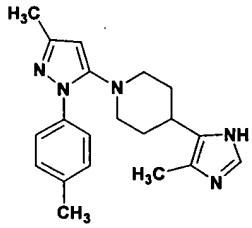
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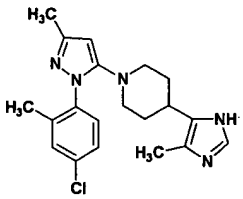
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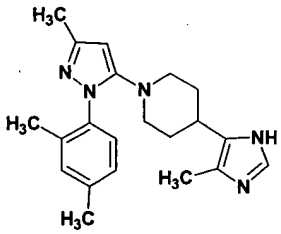
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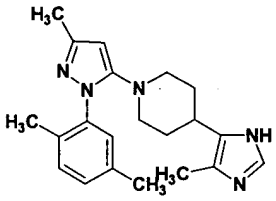
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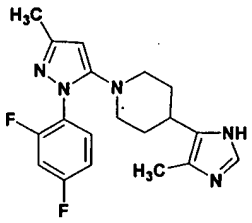
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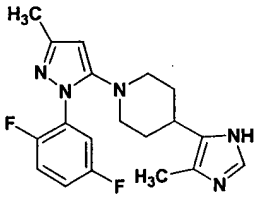
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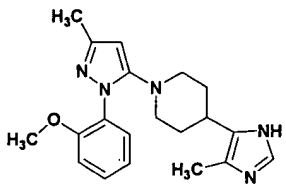
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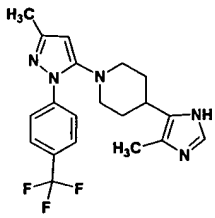
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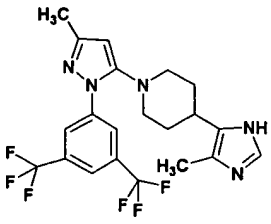
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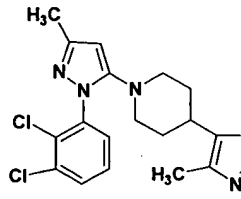
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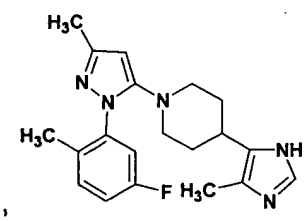
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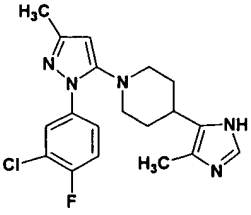
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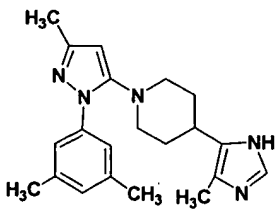
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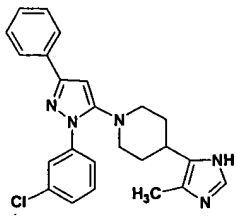
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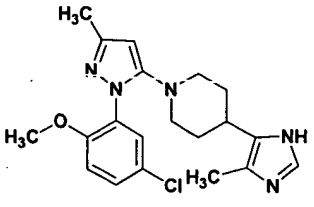
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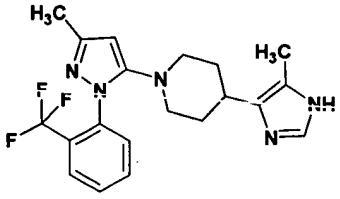
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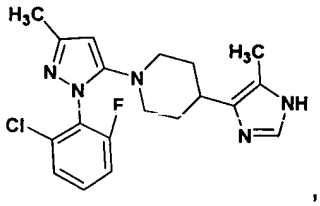
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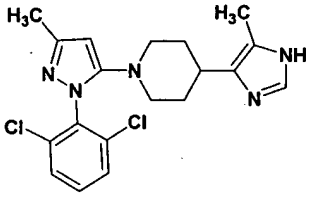
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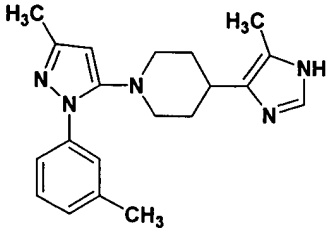
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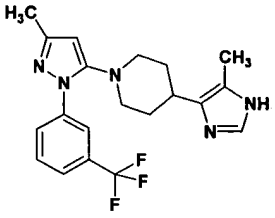
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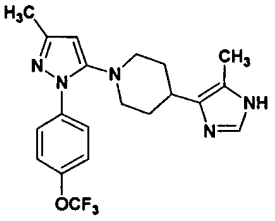
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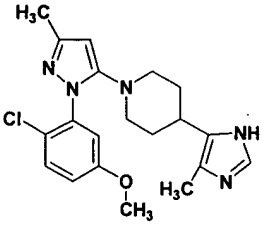
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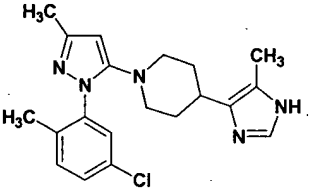
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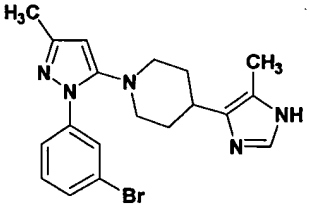
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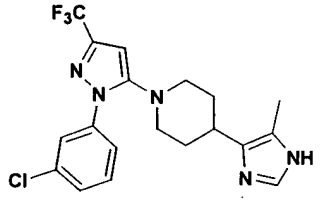
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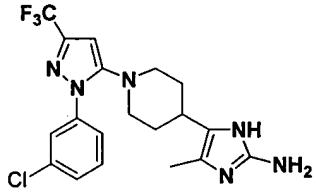
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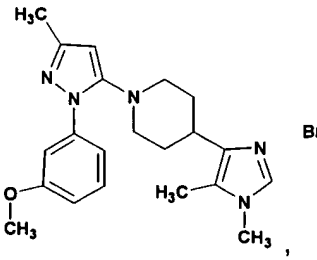
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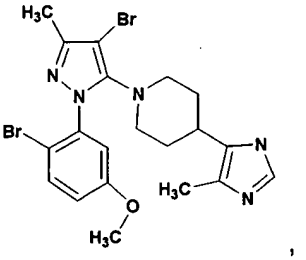
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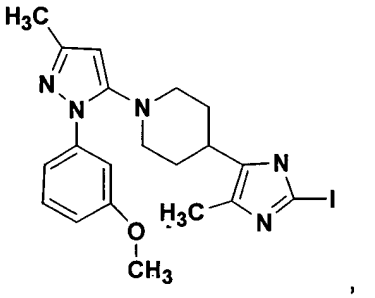
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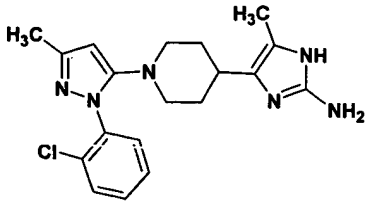
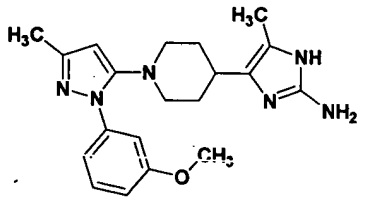
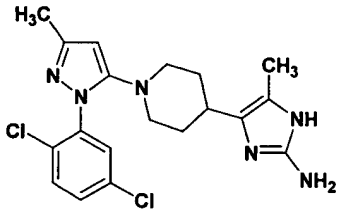
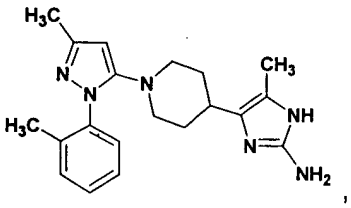
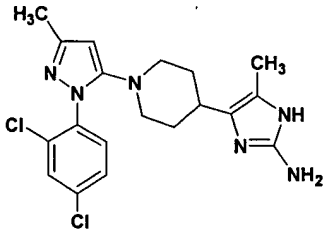
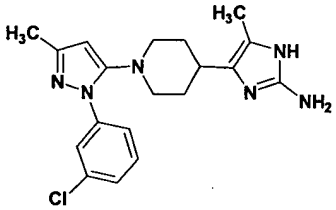
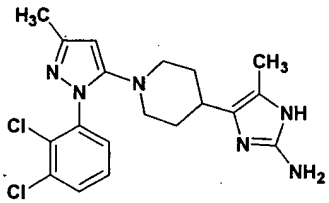
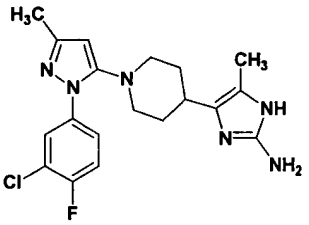
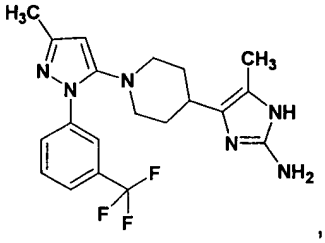
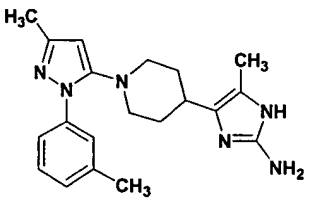
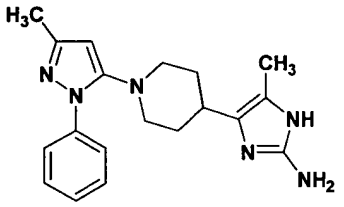
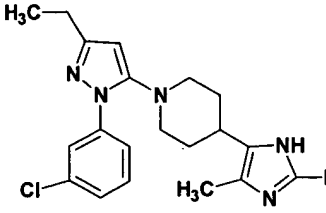
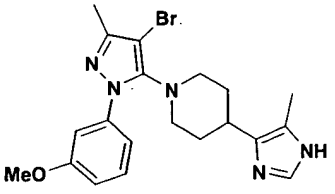

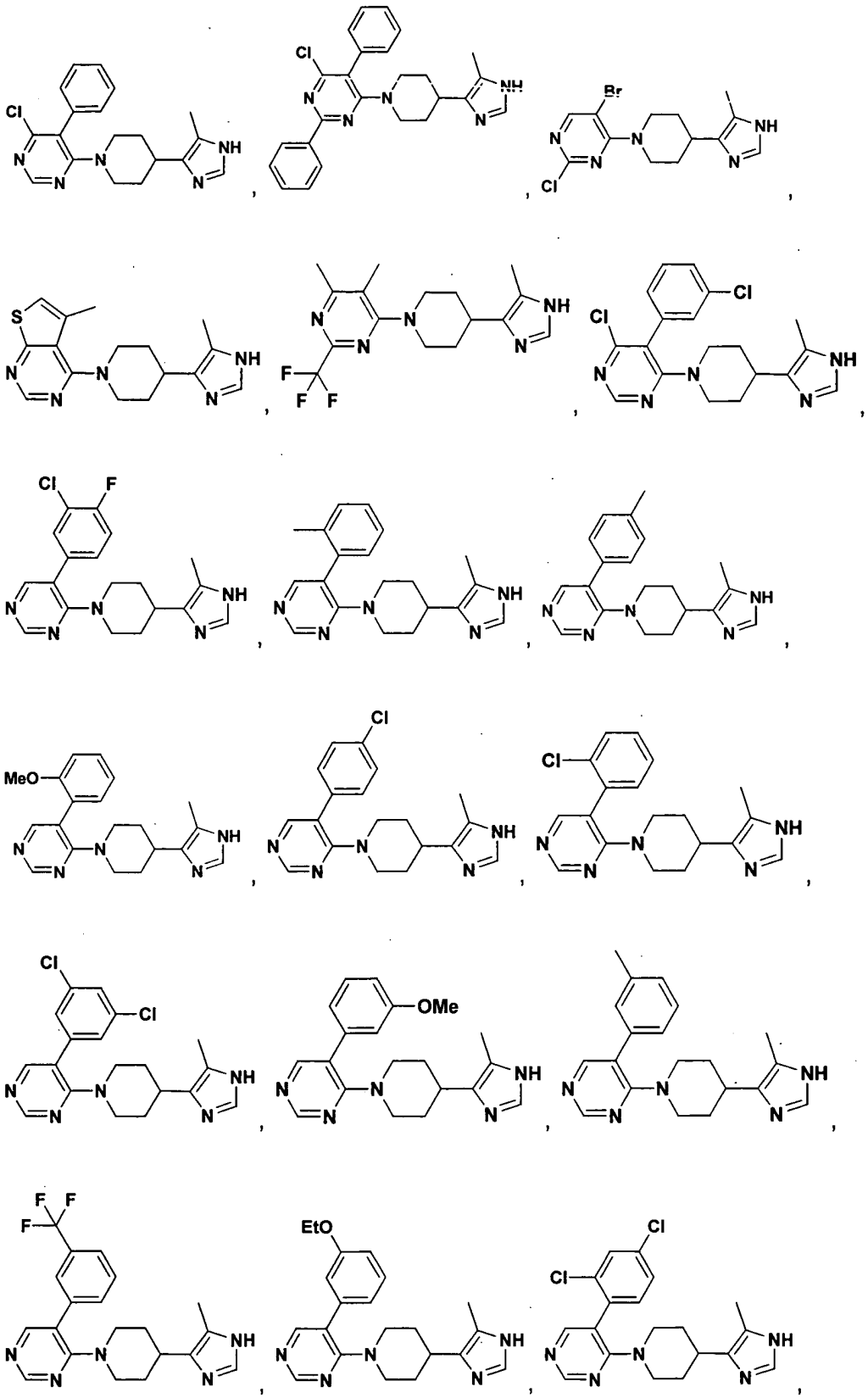

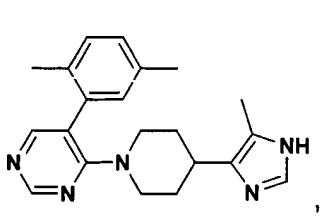
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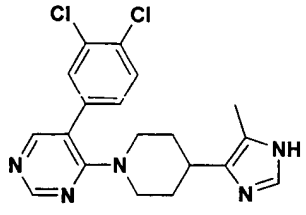
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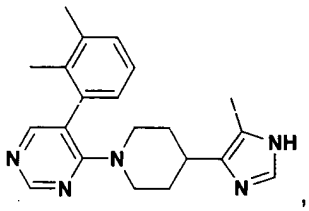
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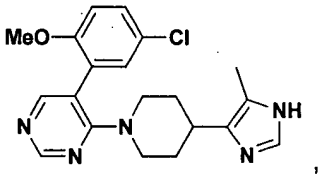
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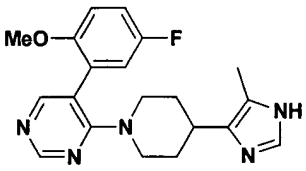
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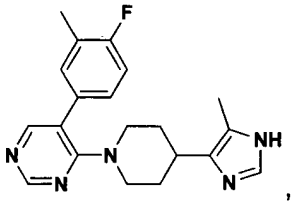
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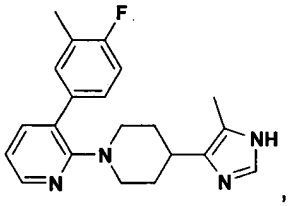
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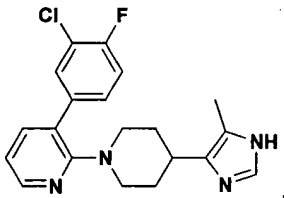
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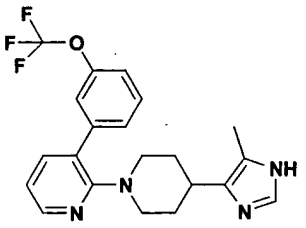
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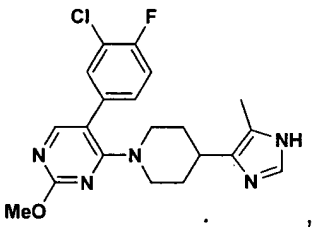
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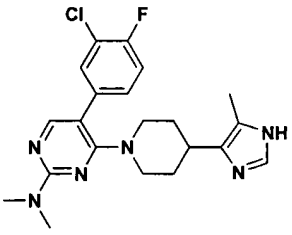
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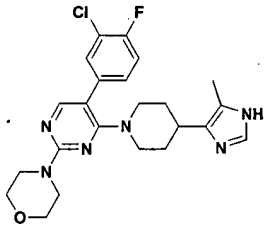
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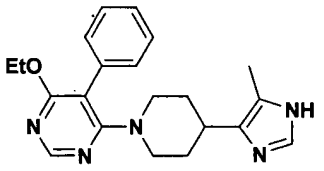
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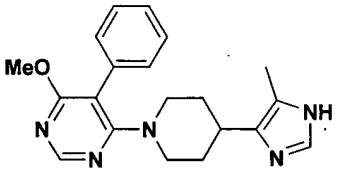
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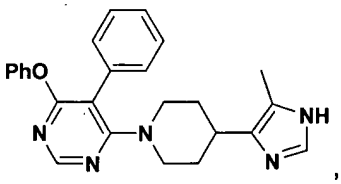
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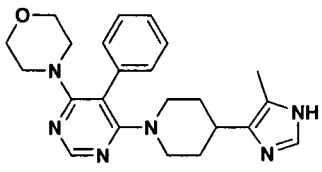
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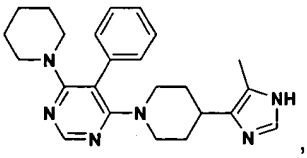
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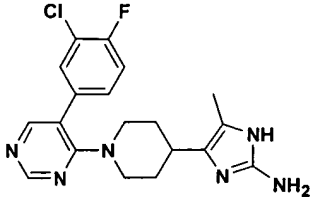
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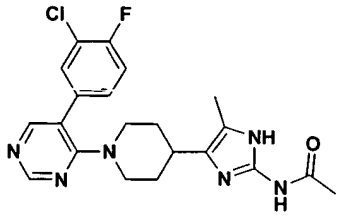

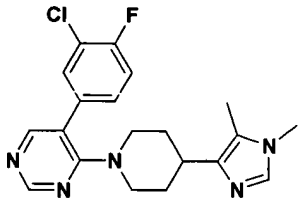

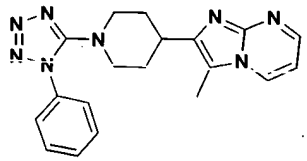

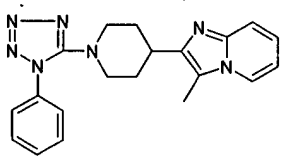

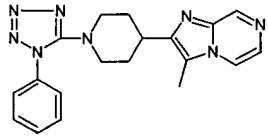

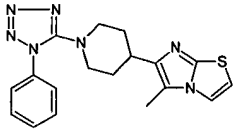

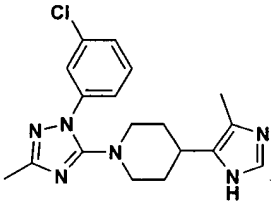

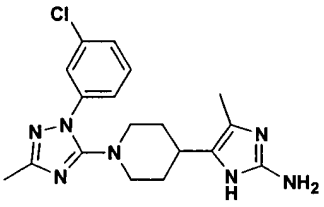

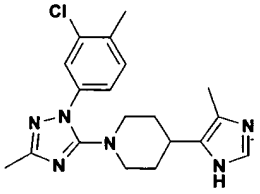

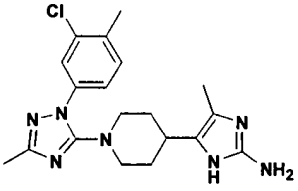

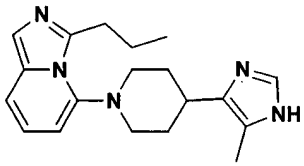

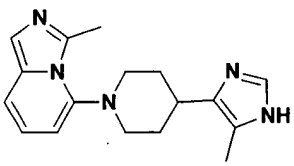

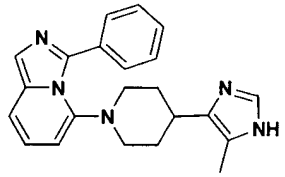

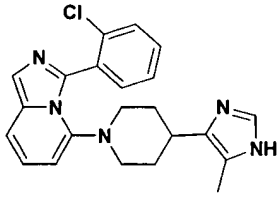

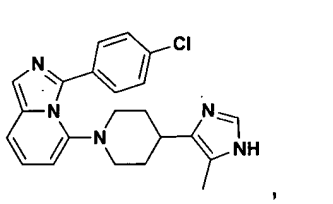

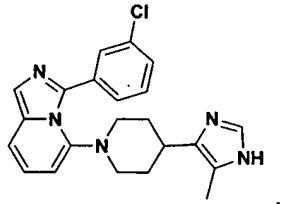

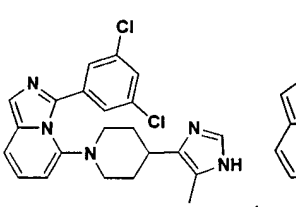

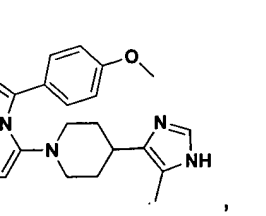

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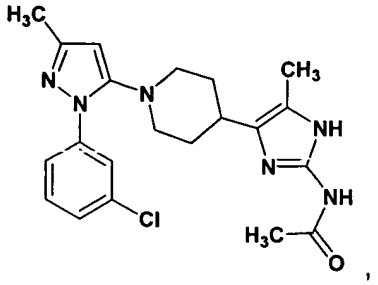
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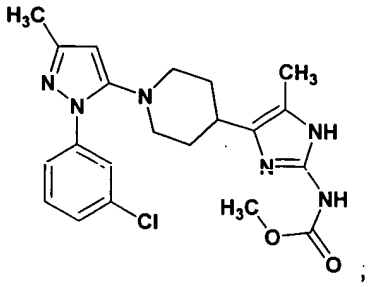
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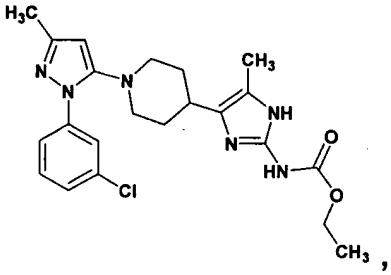
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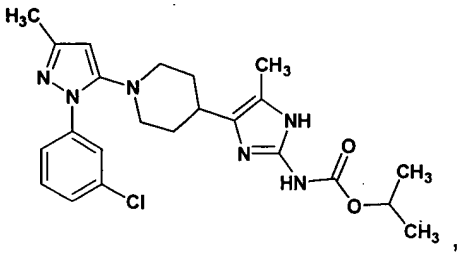
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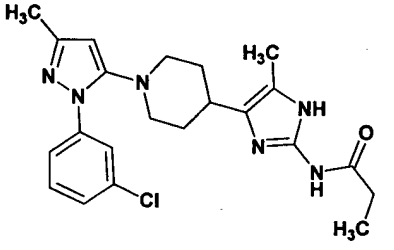
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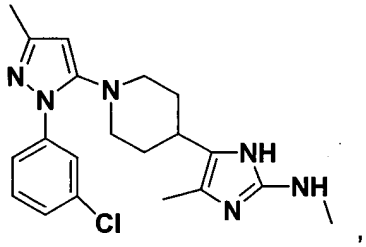
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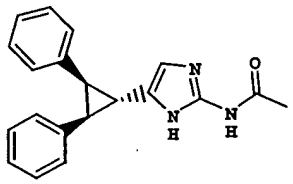
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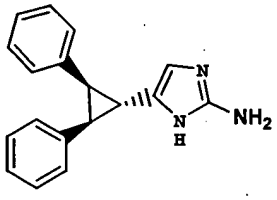
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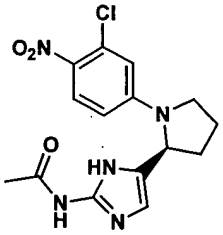
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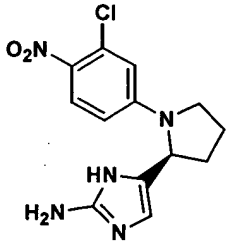
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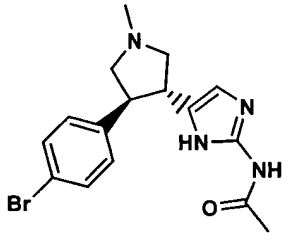
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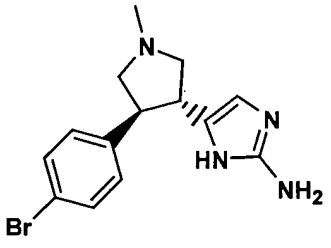
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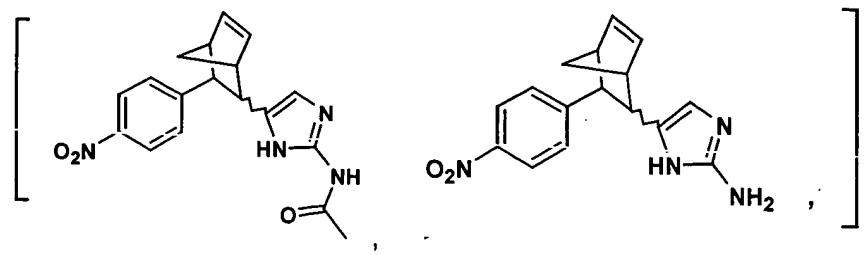

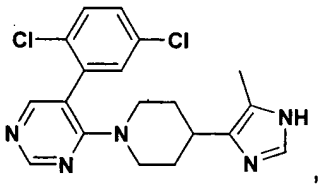

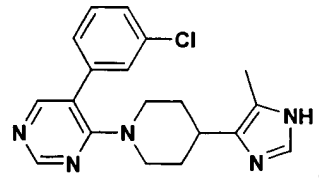

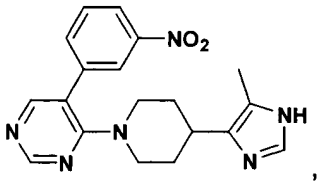

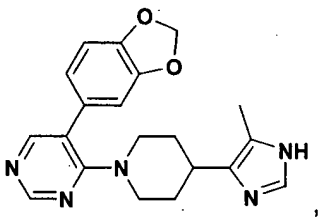

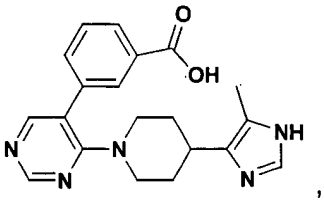

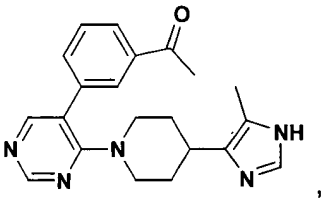

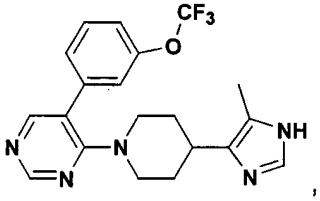

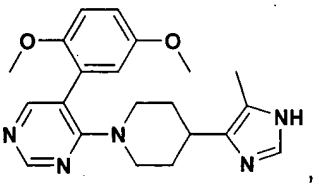

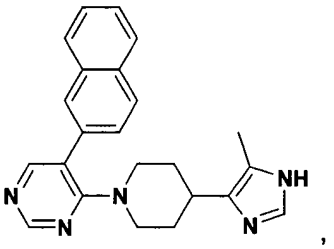

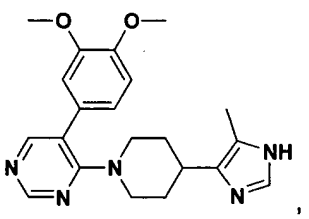

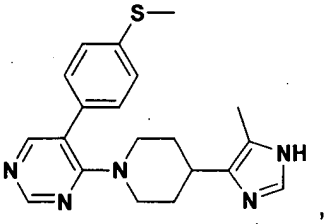

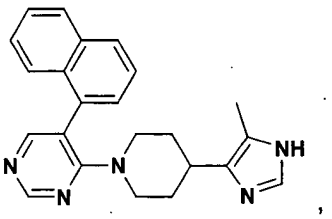

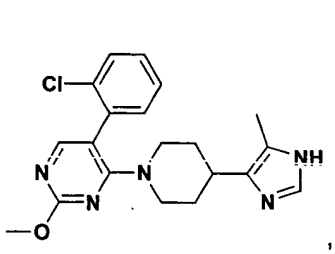
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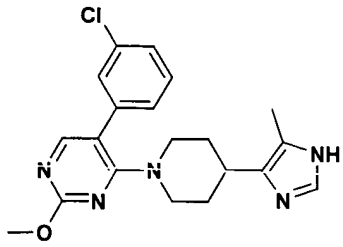
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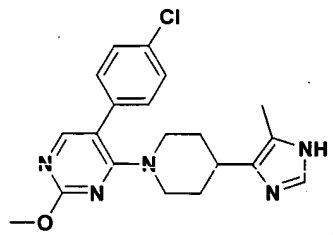
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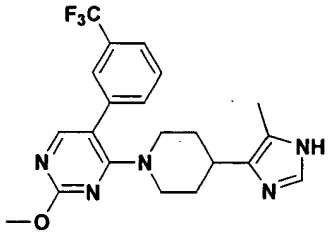
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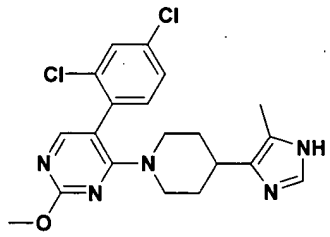
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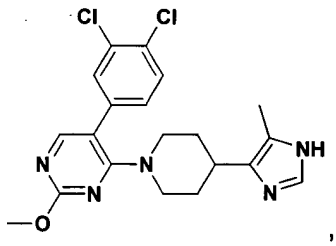
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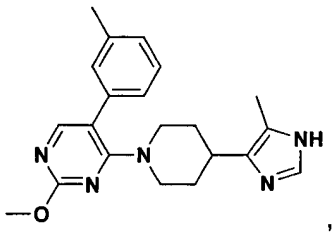
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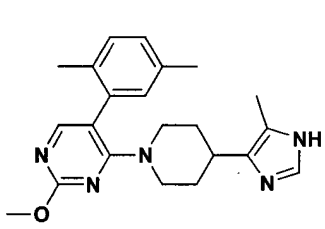
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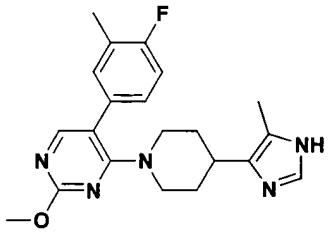
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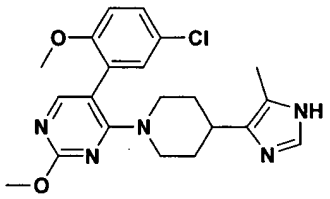
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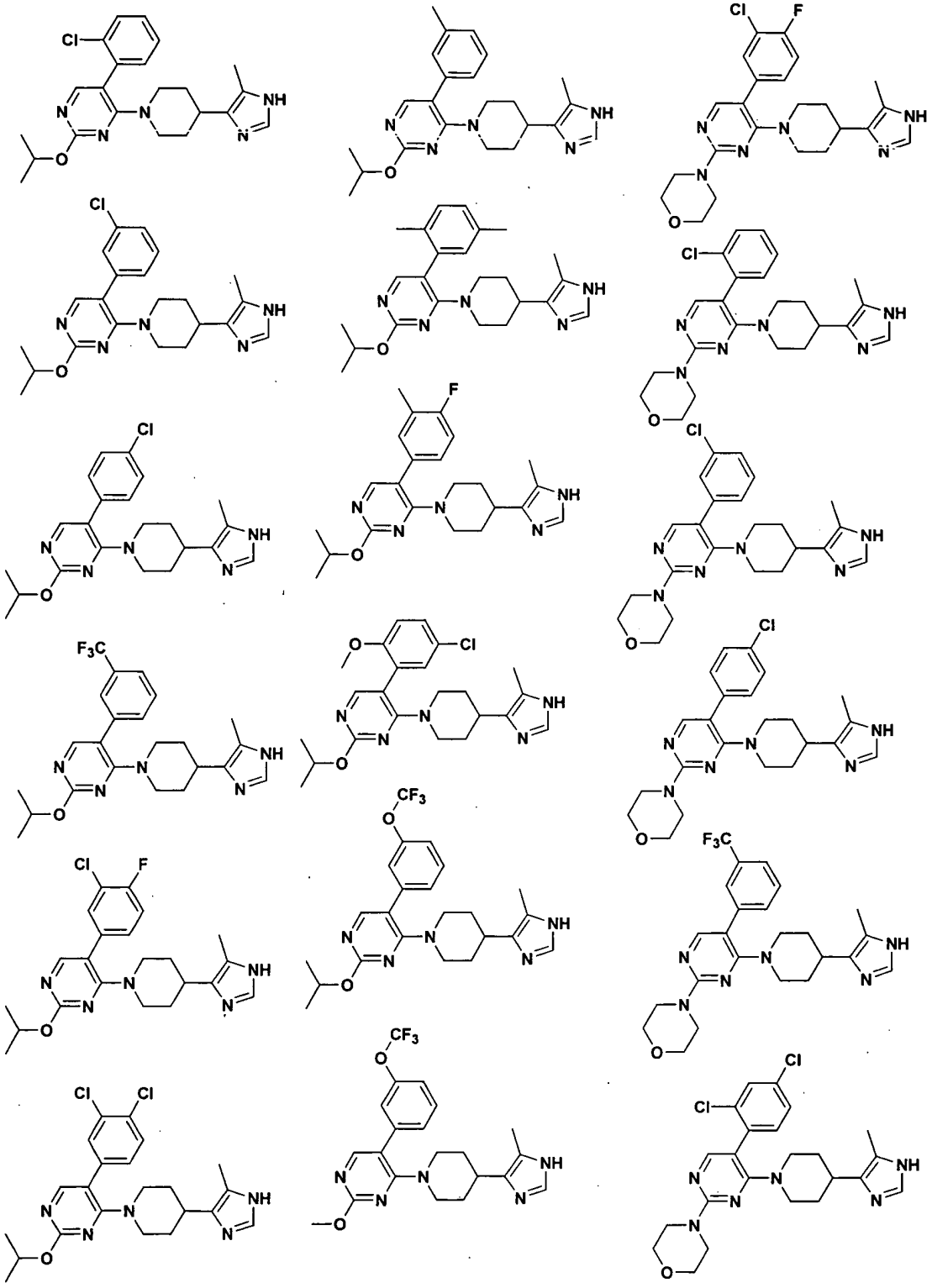
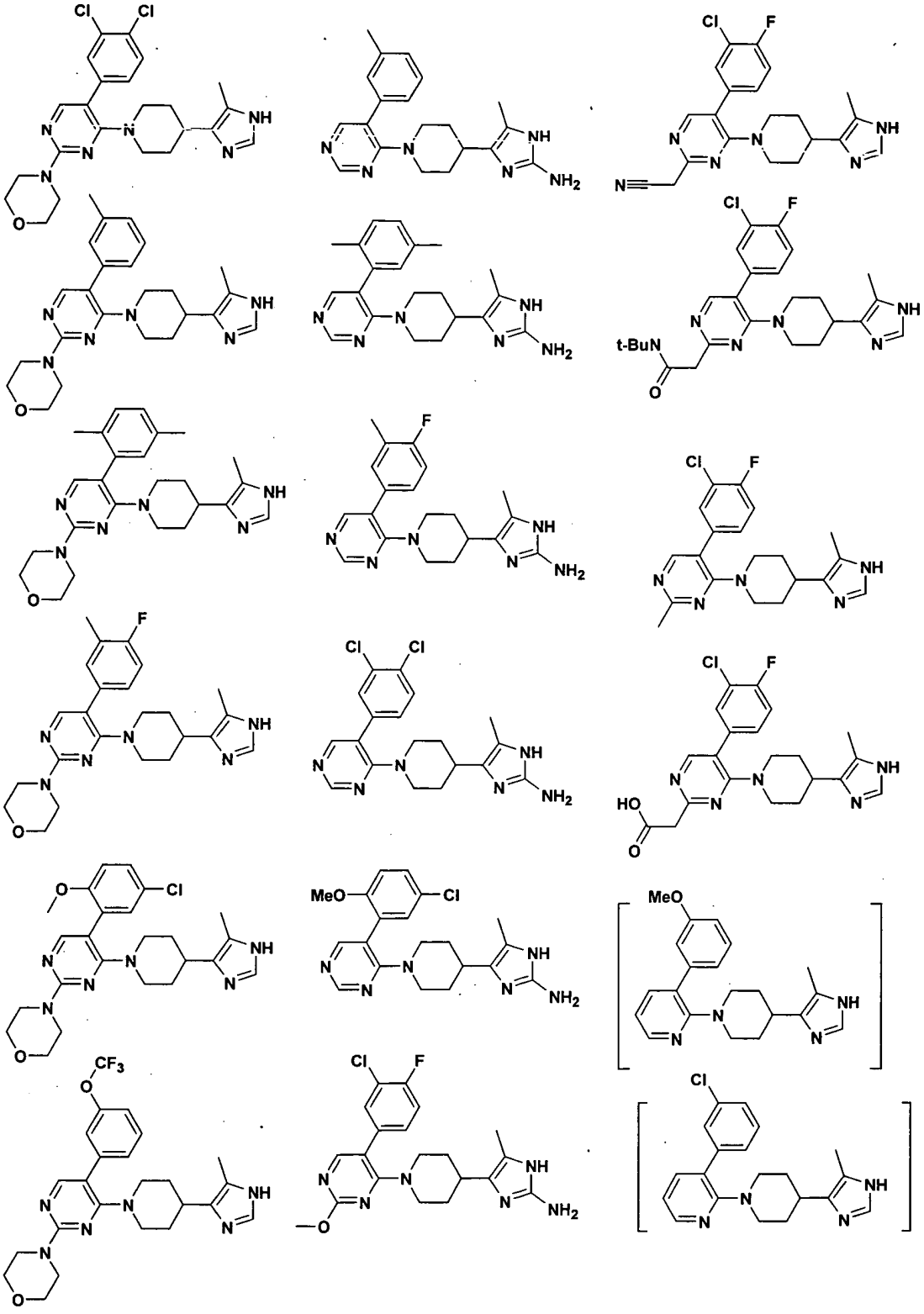
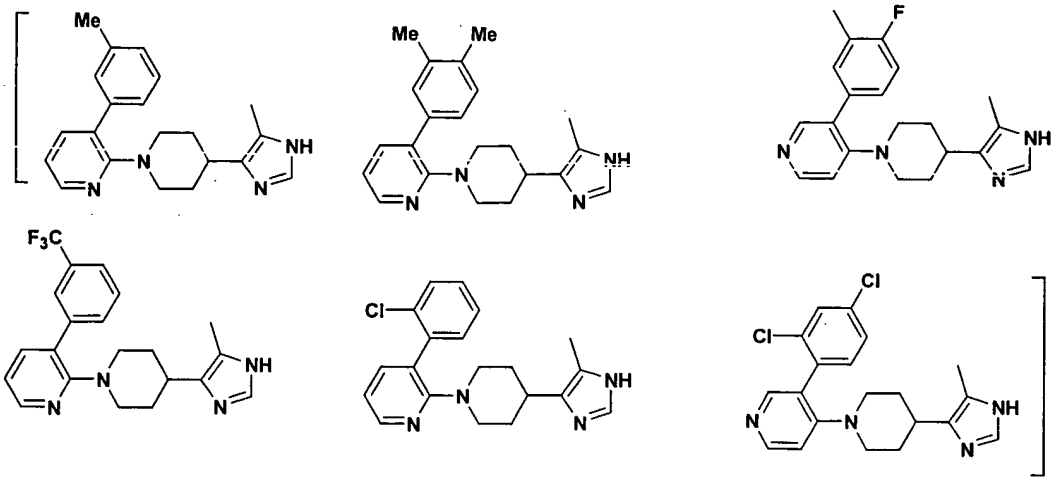
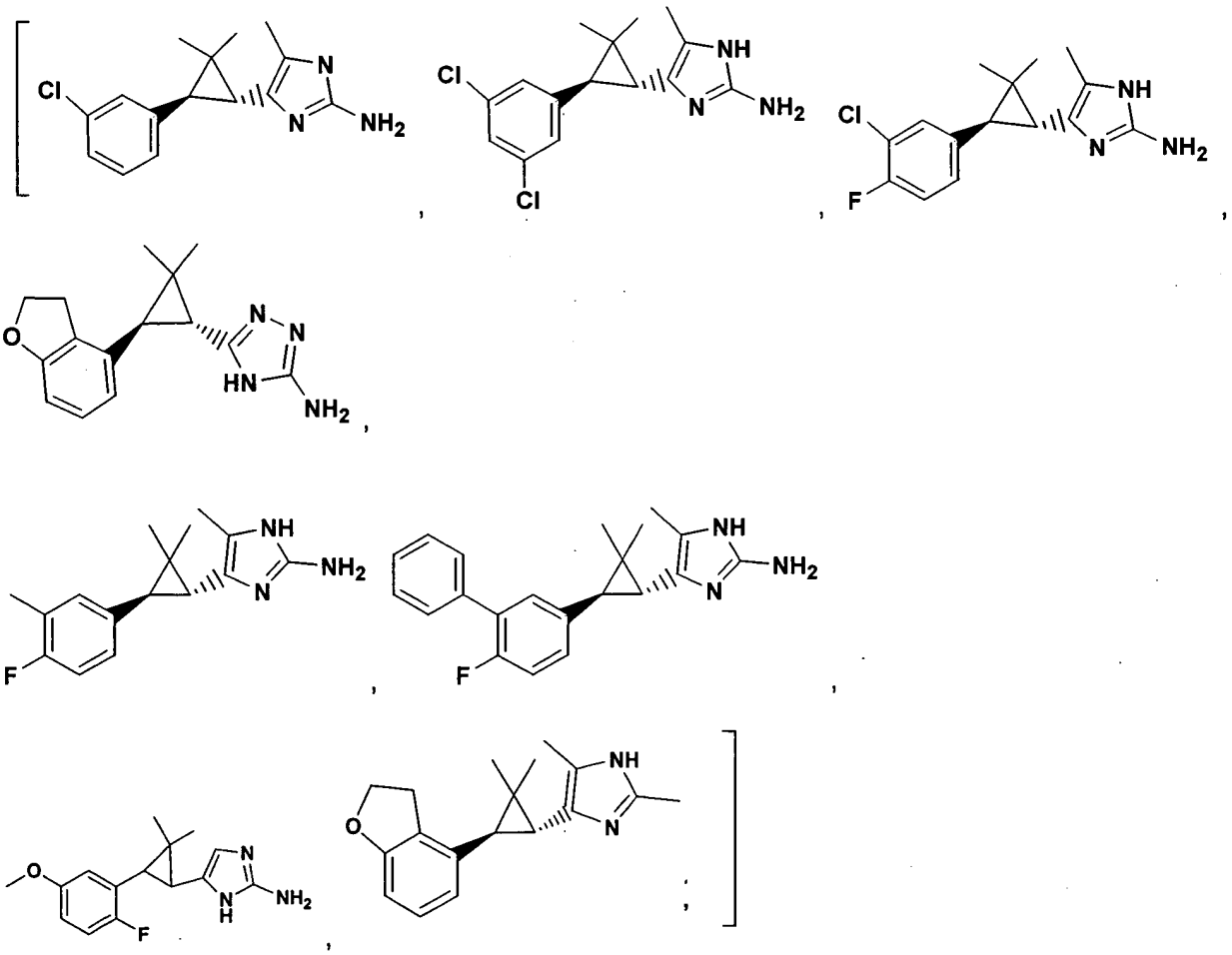






29. (Amended) [The compounds as defined in Claim 1] A compound having the structure



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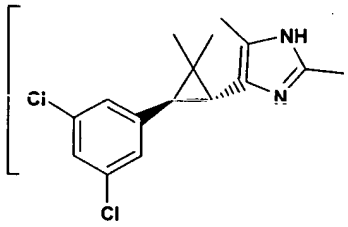
NH
N
Cl
Cl

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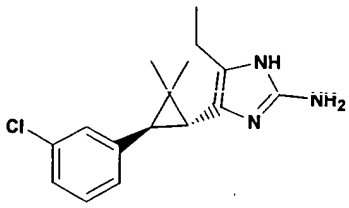
NH
NH2
N
Cl

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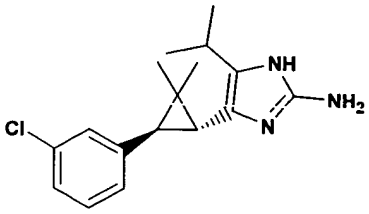
NH
NH2
N
Cl

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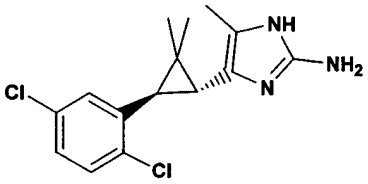
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NH2
N
Cl
Cl

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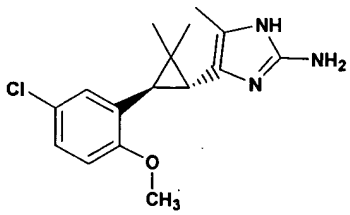
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Cl
O
CH3

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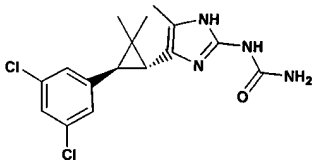
NH
NH
N
NH2
O
Cl
Cl

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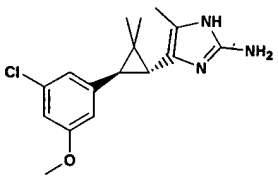
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NH2
N
Cl
O

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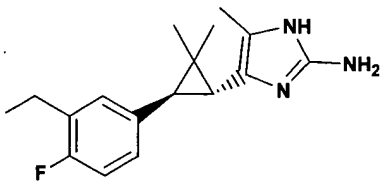
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N
F

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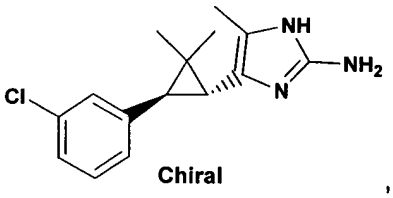
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NH2
N
Cl
Chiral

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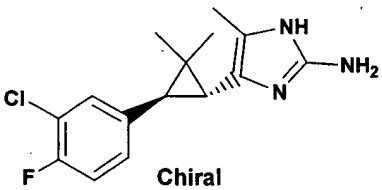
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F
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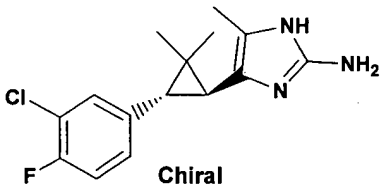
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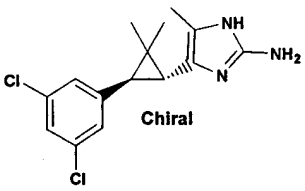
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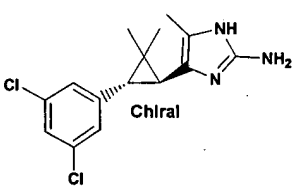
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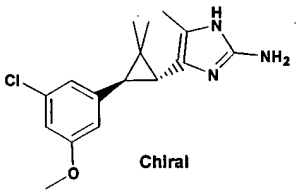
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Chiral

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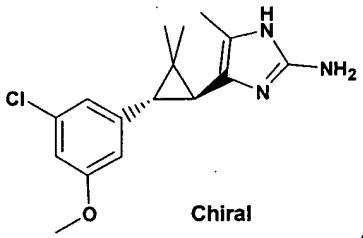
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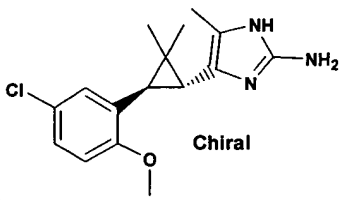
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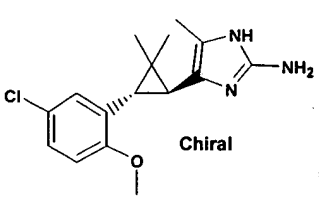
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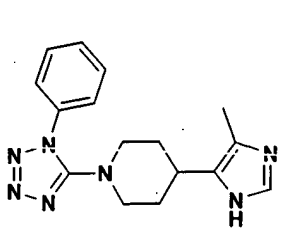
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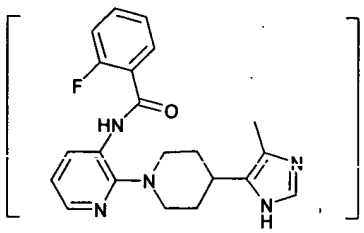
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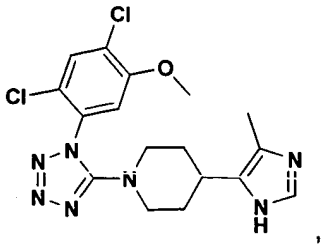
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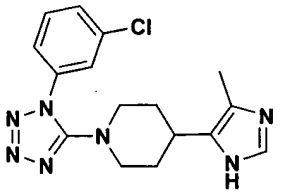
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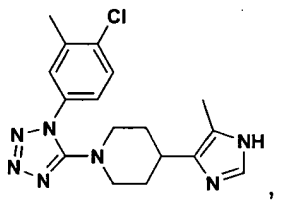
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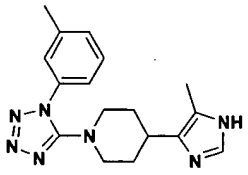
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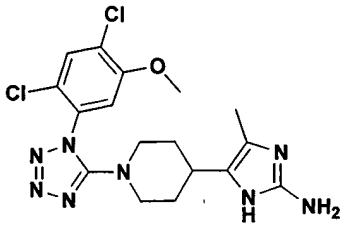
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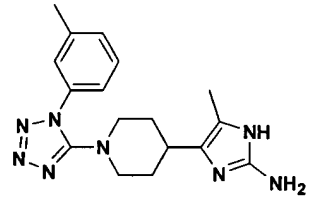
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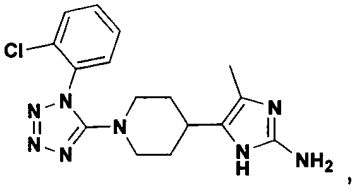
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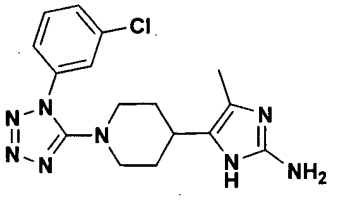
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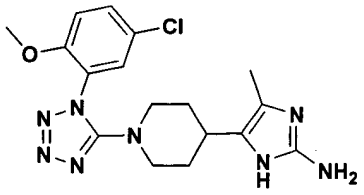
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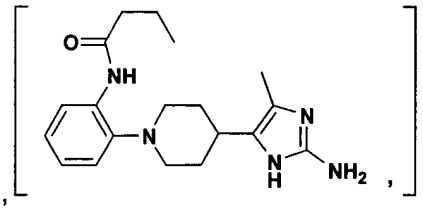
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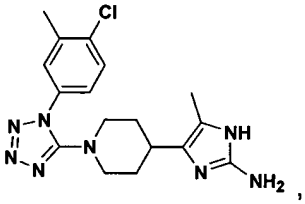
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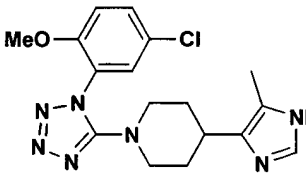
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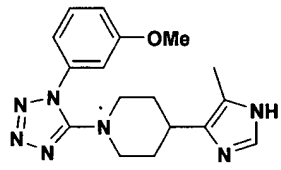
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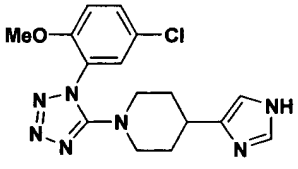
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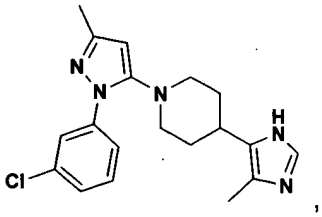
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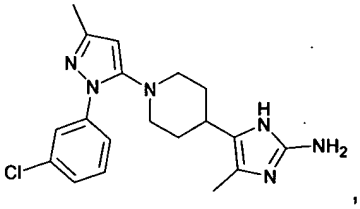
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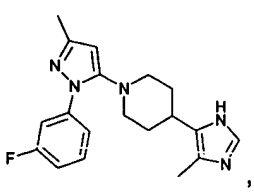
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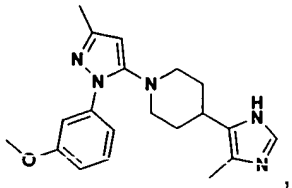
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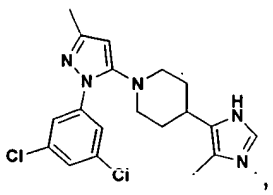
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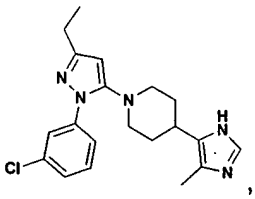
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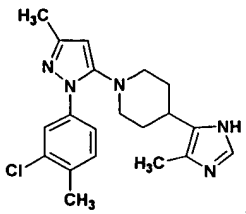
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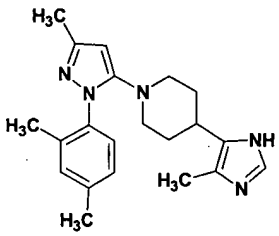
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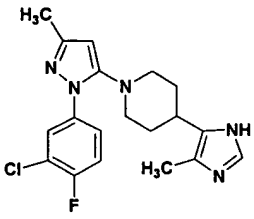
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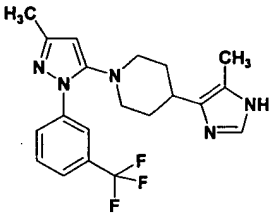
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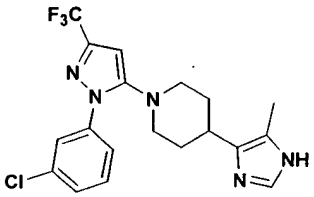
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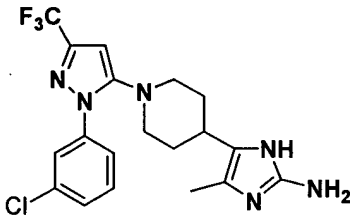
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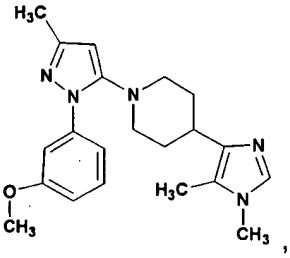
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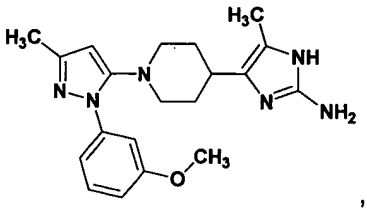
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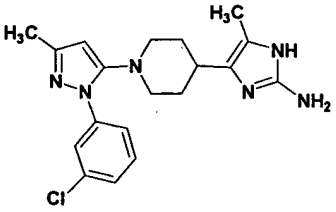
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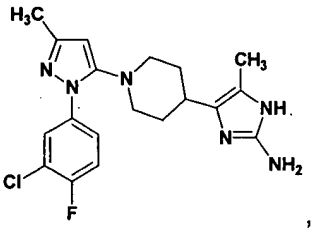
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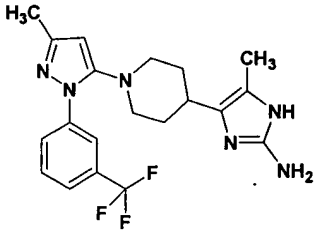
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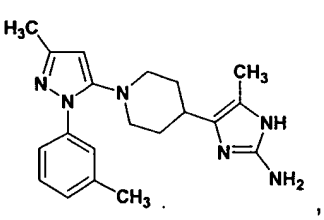
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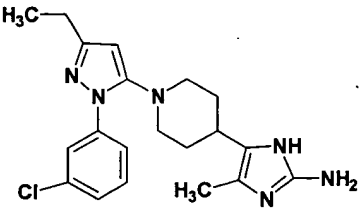
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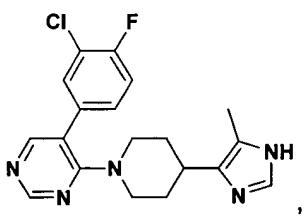
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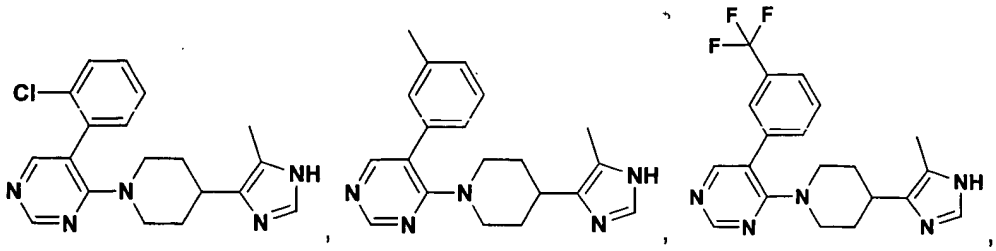

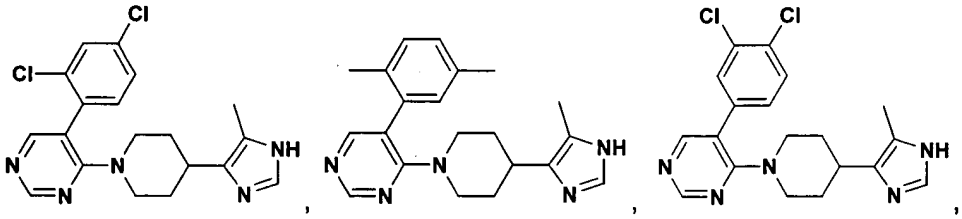

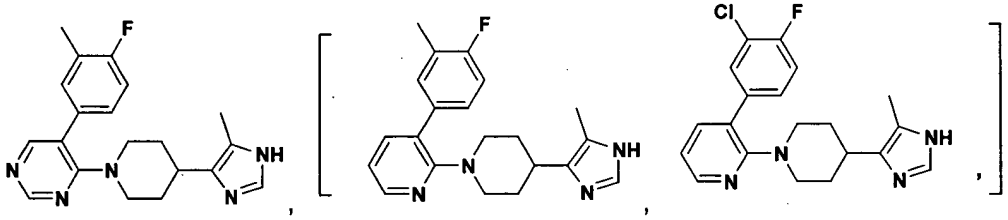

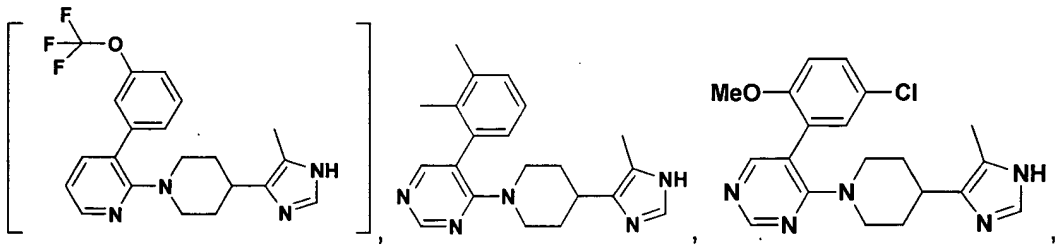

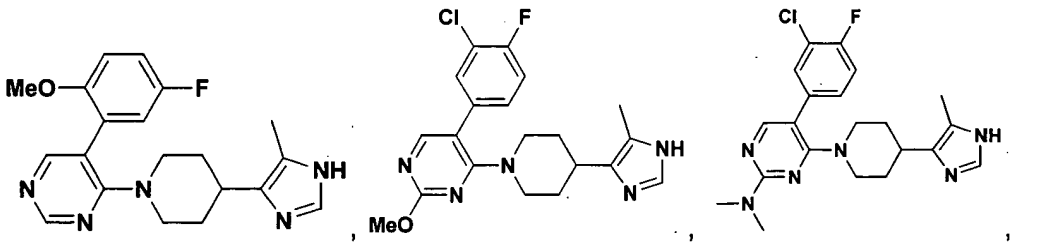

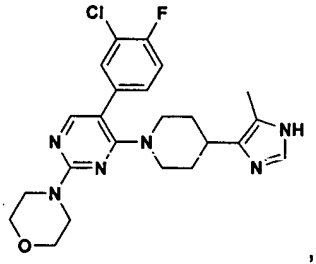
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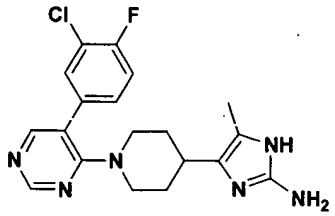
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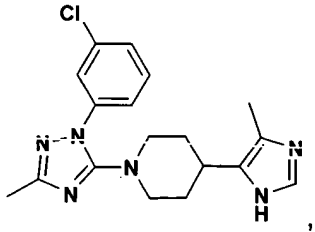
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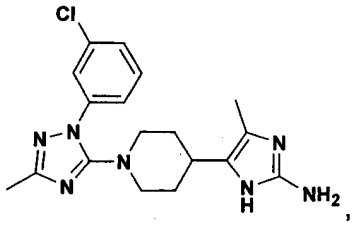
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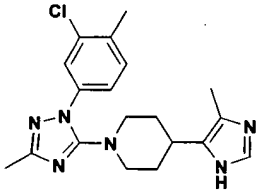
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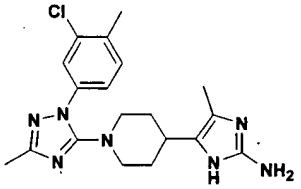
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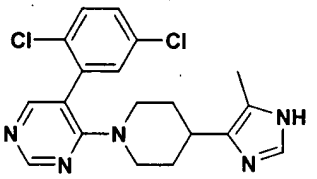
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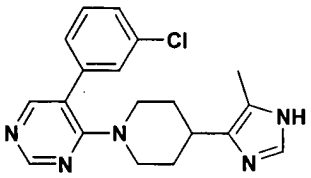
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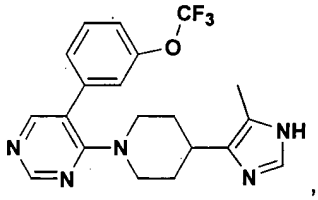
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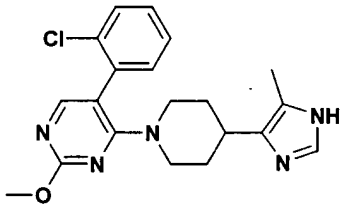
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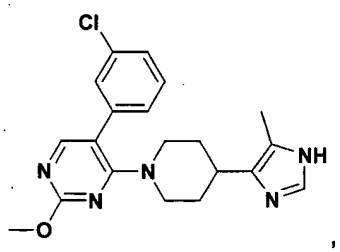
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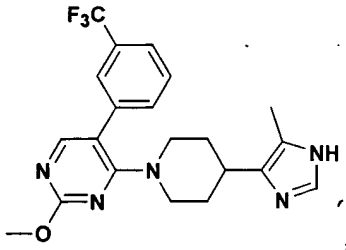
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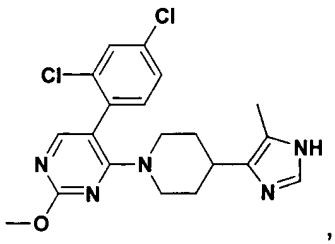
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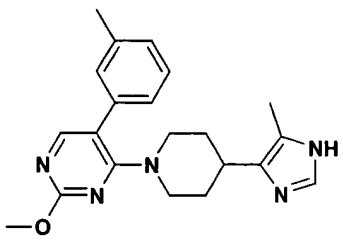
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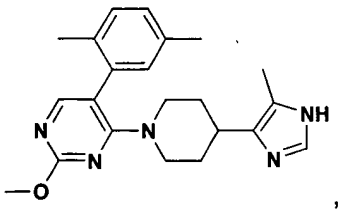
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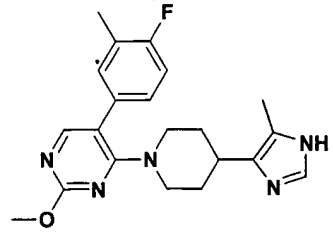
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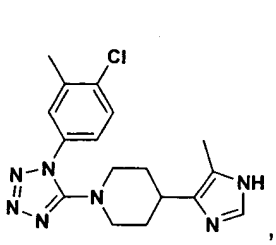
30. [The] A compound [as defined in Claim 1] having the structure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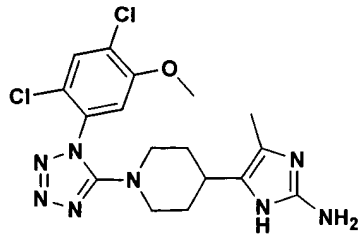
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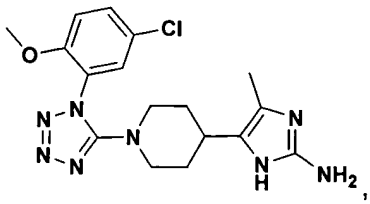
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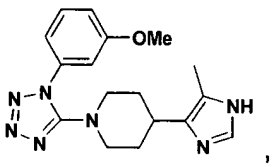
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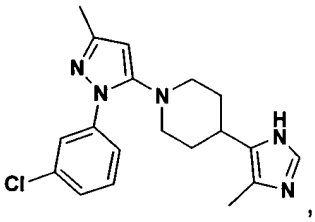
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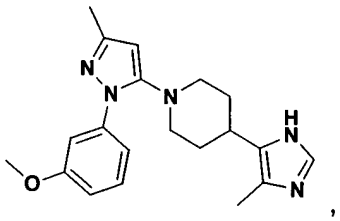
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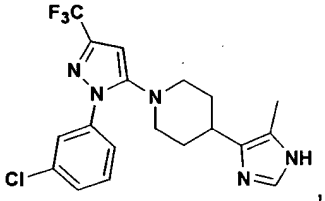
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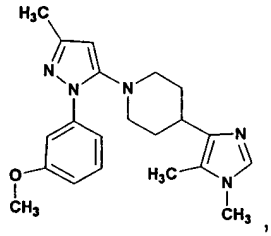
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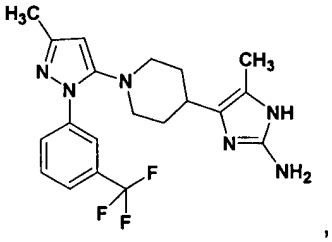
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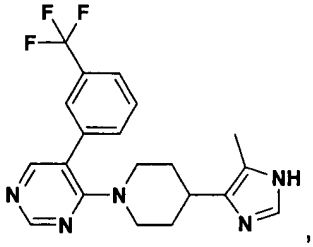
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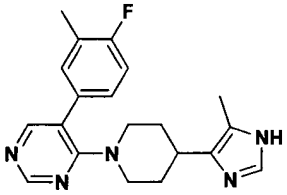
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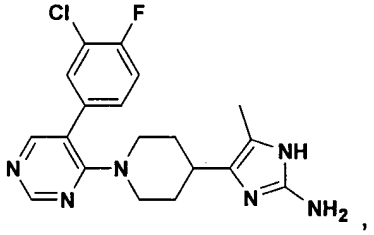
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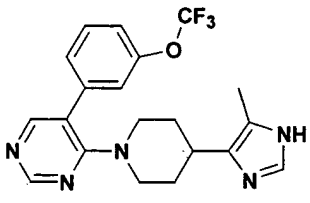
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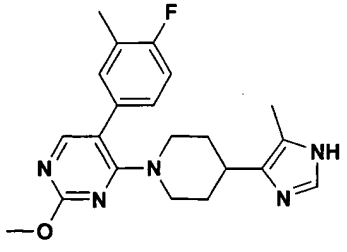
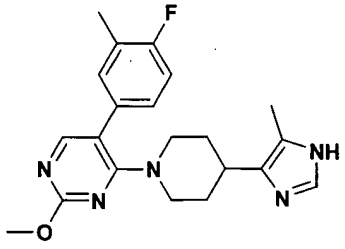
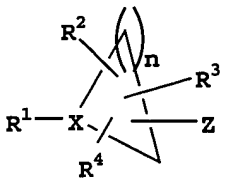


The following Claims 63 to 74 have been added via this Amendment.

63. A compound having the following structure



64. A compound having the structure



wherein n is 4;

X is N;

Z is a heteroaryl group;

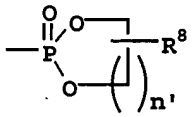
R^1 is heteroaryl, tetrazolyl, pyrazolyl, thiazolyl, pyrimidinyl, imidazole, oxazole, or triazole;

R^6, R^7, R^8, R^{8a} and R^9 are the same or different and are independently hydrogen, alkyl, haloalkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, or cycloheteroalkyl;

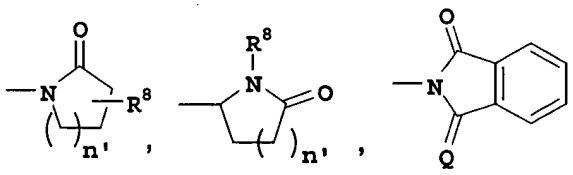
and R^1 may be unsubstituted or substituted with from one to five substituents;

R^2, R^3 and R^4 are the same or different and are independently H, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, (alkyl or aryl)$_3$Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylalkylamino, aryl, arylalkyl, arylamino, aryloxy, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, heteroarylamino, heteroaryloxy, arylthio, arylsulfinyl, arylsulfonyl, thio, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, halogen, haloalkyl, polyhaloalkyl, polyhaloalkoxy, aminothio, aminosulfinyl, aminosulfonyl, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, hydroxy, acyl, carboxy, aminocarbonyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonyl, arylcarbonyloxy,

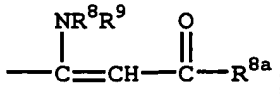
arylcarbonylamino, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroarylcarbonylamino, cyano, nitro, alkenylcarbonylamino, alkynylcarbonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, alkynylaminocarbonylamino, arylaminocarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, aminocarbonylamino, alkylaminocarbonyloxy, alkoxycarbonylamino, l,l-(alkoxyl or aryloxy)$_2$alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring), $S(O)_2R^6R^7$, $-NR^6(C=NR^7)$alkyl, $-NR^6(C=NR^7)$alkenyl, $-NR^6(C=NR^7)$alkynyl, $-NR^6(C=NR^7)$heteroaryl, $-NR^8(C=NCN)$-amino,



pyridine-N-oxide,



(where Q is O or H_2 and n' is 0, 1, 2 or 3) or



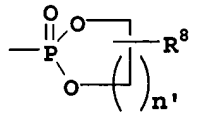
; tetrazolyl, pyrazolyl, pyridyl, thiazolyl, pyrimidinyl, imidazole, oxazole, or triazole, $-PO(R^{13})(R^{14})$, (where R^{13} and R^{14} are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy); and may be optionally independently substituted with from one to five substituents, which may be the same or different;

including pharmaceutically acceptable salts thereof, prodrugs thereof, and all stereoisomers thereof; with the proviso that where Z is imidazole-4-yl, 5-alkylimidazol-4-yl or 5-cyclohexylimidazol-4-yl, then R^1 cannot be benzoxazole, benzthiazole, benzimidazole or pyridine.

65. The compound as defined in Claim 64 wherein Z is imidazole, aminoimidazole, alkylimidazole, alkylthioimidazole, alkylthio(amino)imidazole, amino-(alkyl)imidazole, oxazole, (alkanoylamino)imidazole, thiazole, benzimiazole, aminothiazole, aminooxazole, aminooxadiazole, dialkylimidazole, alkyl(alkanoylamino)imidazole, alkyl(amino)imidazole, arylaminocarbonylamino(alkyl)imidazole, alkoxycarbonylamino(alkyl)imidazole, alkylcarbonylamino(alkyl)imidazole, aminotriazole or diaminopyrimidine.

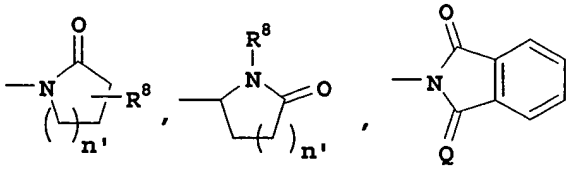
66. The compound as defined in Claim 1 wherein the R^1 group may be substituted within from one to five of the following groups:

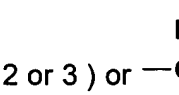
alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, (alkyl or aryl)$_3$Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylalkylamino, aryl, arylalkyl, arylamino, aryloxy, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, heteroarylamino, heteroaryloxy, arylthio, arylsulfinyl, arylsulfonyl, thio, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, halogen, haloalkyl, polyhaloalkyl such as CF_3 and CF_3CH_2, polyhaloalkyloxy such as CF_3O and CF_3CH_2O, aminothio, aminosulfinyl, aminosulfonyl, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, hydroxy, acyl, carboxy, aminocarbonyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonyl, arylcarbonyloxy, arylcarbonylamino, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroarylcarbonylamino, cyano, nitro, alkenylcarbonylamino, alkynylcarbonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, alkynylaminocarbonylamino, arylaminocarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, aminocarbonylamino, alkylaminocarbonyloxy, l,l-(alkoxyl or aryloxy)$_2$alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring, such as l,3-dioxane or l,3-dioxolane), $S(O)_2R^6R^7$, $-NR^6(C=NR^7)$alkyl,



$NR^6(C=NR^7)$alkenyl, $-NR^6(C=NR^7)$alkynyl,

$NR^6(C=NR^7)$heteroaryl, $-NR^8(C=NCN)$-amino, pyridine-N-oxide,

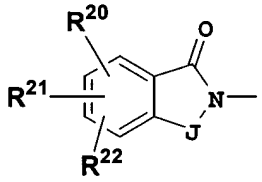


(where Q is O or H_2 and n' is 0,1,2 or 3) or  ; tetrazolyl, pyrazolyl, pyrydyl, thiazolyl, pyrimidinyl, imidazole, oxazole or triazole; $-PO(R^{13})(R^{14})$, (where R^{13} and R^{14} are independently

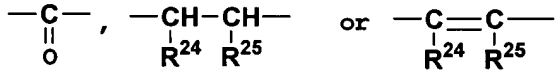
alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy);

R^6, R^7, R^8, R^{8a} and R^9 are independently hydrogen, alkyl, haloalkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl or cycloheteroalkyl, which substituents may be the same or different from each other and may be the same or different from the base R^1 group.

67. The compound as defined in Claim 64 wherein R^1 is substituted with one to five of the following substituents: alkyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, alkylcarbonylamino, heteroaryl, halo, aryl, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, guanidinyl, nitro, cycloheteroalkyl, aryloxycarbonylamino, heteroaryloxylcarbonylamino, uriedo (where the uriedo nitrogens may be substituted with alkyl, aryl or heteroaryl), heterocyclylcarbonylamino (where the heterocycle is connected to the carbonyl group
via a nitrogen or carbon atom), alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,



,

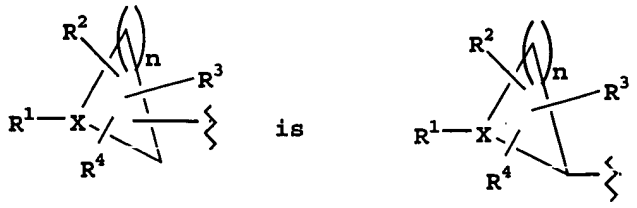
Where J is: CHR^{23},  ;

R^{23}, R^{24} and R^{25} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

R^{20}, R^{21}, R^{22} are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl; and these preferred substituents may either be directly attached to R^1, or attached via an alkylene chain at an open position, which substituents may be the same or different from each other and may be the same or different from the base R^1 group.

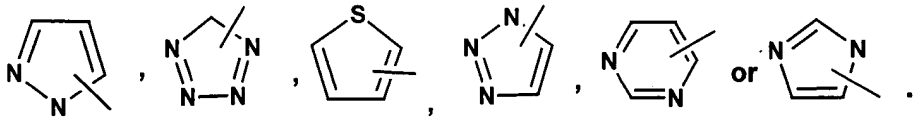
68. The compound as defined in Claim 64 wherein Z is imidazole, aminoimidazole, alkylimidazole, alkylthioimidazole, alkylthio(amino)imidazole, amino(alkyl)imidazole or (acetylamino)imidazole.

69. The compound as defined in Claim 64 wherein the moiety



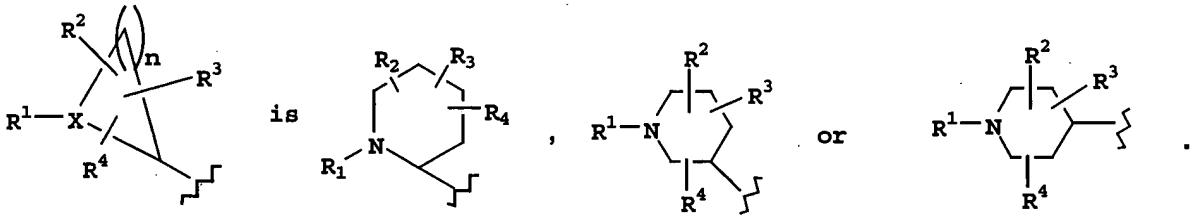
70. The compound as defined in Claim 64 wherein R^2 and R^3 are independently H, lower alkyl, lower alkoxy or aryl, and R^4 and R^5 are each hydrogen.

71. The compound as defined in Claim 64 wherein R^1 is

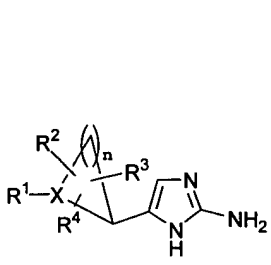


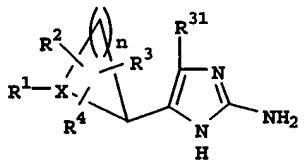
72. The compound as defined in Claim 64 wherein R^1, R^2, R^3 and/or R^4 may be joined together with the N atom and/or carbons to which they are attached to form a non-aromatic ring.

73. The compound as defined in Claim 64 wherein

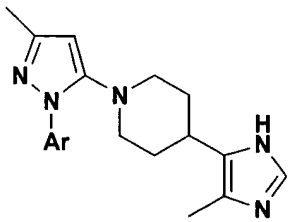


74. The compound as defined in Claim 64 having the structure

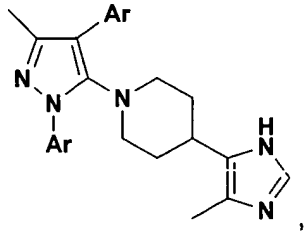


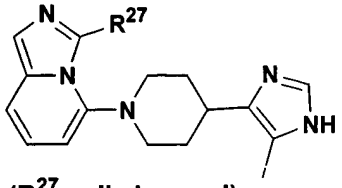


(R^{31} = alkyl, haloalkyl, aryl, heteroaryl)

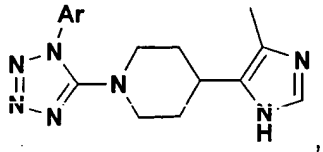


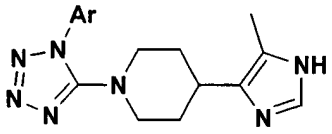
(Ar = aryl or heteroaryl)

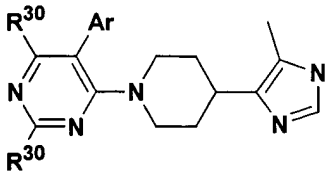




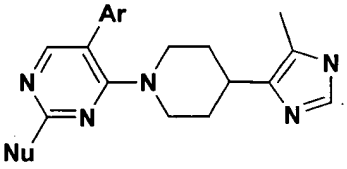
(R^{27}= alkyl or aryl)



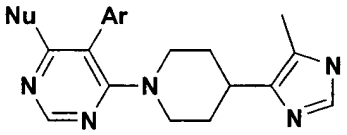


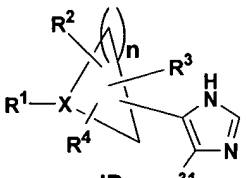


(R^{30}= alkyl or halo)



(Nu = alkyl-O, alkyl NH, $(alkyl)_2N$, alkyl-S or alkyl)





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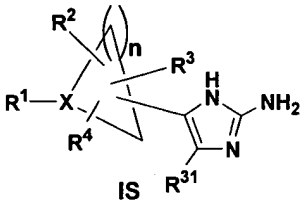

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